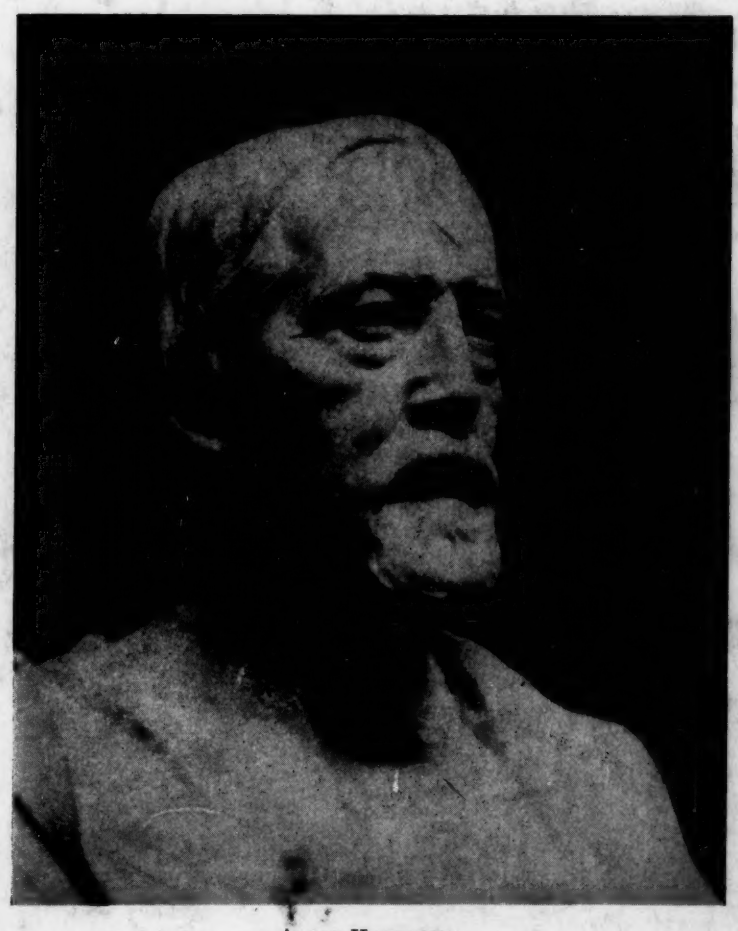
DIABETES

The Journal of the American Diabetes Association



ADOLF KUSSMAUL

VOLUME 4, NUMBER 1-6

JANUARY-FEBRUARY 1955 -
November-December 1955

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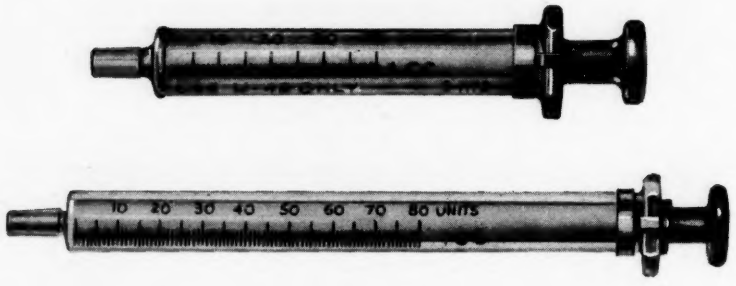

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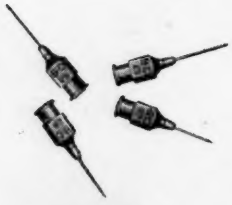

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Correlation of Beta-cell Granulation with Extractable Insulin of the Pancreas

Studies in Adult Human Diabetics and Nondiabetics

*W. Stanley Hartroft, M.D., Ph.D.,**
Gerald A. Wrenshall, Ph.D.†
Toronto

The authors have previously reported the degree of correlation between the amount of extractable insulin and the numbers of beta cell granules present in the pancreases of a series of ninety-two patients coming to autopsy in the Department of Pathology, University of Toronto (Hartroft;[1] Wrenshall, Bogoch, and Ritchie[2]). One-half the patients were known diabetics and the other half nondiabetics. The coefficient of linear correlation between the amounts of extractable insulin and the beta cell granulation, although statistically significant, was low (0.48). Since the appearance of these reports, we have not only added more cases to the series, but also have obtained new histologic data for all cases. The technic of measuring extractable insulin in the pancreases of the cases added to the series since 1950 was the same as that employed for the original members (Wrenshall, Bogoch, and Ritchie[2]).

We are now able to report that the coefficient of linear correlation between numbers of beta cell granules, estimated in sections stained by Wilson's modification[3] of the Gomori aldehyde-fuchsin method,[4] and the amount of extractable insulin obtained from pancreases of 86 nondiabetic human subjects is 0.584; for 80 diabetics the comparable figure is 0.680. Because these positive correlation coefficients differ very significantly from zero, they provide strong objective evidence in support of the thesis that, in both diabetic and nondiabetic man, beta cell granules represent or contain a form of pancreatic insulin or insulin precursor. This concept has already been well established by a variety of experiments involving animals (Barron;[5] Dohan and Lukens;[6] Barron and State;[7] Wrenshall, Collins-Williams, and Hartroft;[8] Campbell and Hartroft;[9] and others). Bell's[10] histologic findings in pancreases of 995 cases of diabetes and of 250 nondiabetics, together with our data presented here, permit the conclusion that beta granules in man contain insulin or a precursor thereof.

From the Banting and Best Department of Medical Research, University of Toronto.

Presented in part by the authors at the annual meeting of the American Society for Experimental Pathology, April 7, 1953, Chicago, and published in abstract form in Federation Proc. *12*:390-91, 1953.

Supported in part by grants from the National Research Council of Canada and the Banting Research Foundation.

*Formerly Professor in the Banting and Best Department of Medical Research, and Associate in the Department of Pathology, University of Toronto; now Chairman of the Department of Pathology, Washington University, St. Louis, Missouri.

†Associate Professor in the Banting and Best Department of Medical Research, University of Toronto.

METHODS

Insulin Assay

The pancreas was carefully dissected free at autopsy and weighed. A block (3 mm. thick) from the midsection was immersed in Bouin's fixative; the remainder was again weighed and extracted for insulin by the method of Scott and Fisher.[11] Concentrations of insulin in the resulting extracts were estimated by a mouse-convulsion method of assay that meets all the requirements recommended by Bliss.[12] For the purpose of this report, the results have been expressed in units of extractable insulin per gram of pancreas.

Beta Cell Estimates

After eighteen to twenty-four hours in Bouin's fixative, blocks of pancreas were dehydrated and cleared in absolute isopropyl alcohol with the aid of a Technicon. Infiltration of wax was completed in a vacuum and the paraffin-embedded blocks of tissue were sectioned at a thickness of three micra. The procedure for selectively staining the granules in beta cells is the aldehyde-fuchsin technic of Gomori[14] modified as follows by Wilson[3] in our laboratory.

Sections were decerated in the usual manner and washed briefly in water. They were oxidized by immersion for two minutes in 0.3 per cent potassium perman-

ganate in 0.3 per cent sulfuric acid. This step was followed by decolorization in 4 per cent sodium bisulfite, after which the sections were washed for one minute in running tap water. Beta cell granules in the sections were stained deep purple by immersion in aldehyde-fuchsin reagent for five minutes at room temperature. Sections were rinsed in 95 per cent ethanol until free of excess stain and *vigorously* washed in running tap water until, to the naked eye, they appeared pale purple or even colorless. They were dehydrated rapidly and cleared to be examined microscopically. At this stage the islets stood out sharply owing to their intense purple color, produced by the stained granules of the beta cells. The sections were decerated a second time, rinsed in tap water, and stained by immersion in Halmi's solution for four minutes. They were rinsed in 2 per cent acetic acid to remove excess stain, dehydrated, cleared in xylol, and finally mounted in balsam. This procedure stains the beta cell granules deep purple, but leaves the alpha cell granules colorless or red. Acinar tissue appears green, zymogen granules red-purple, elastic tissue deep purple, and nuclei are rust-colored.

The aldehyde-fuchsin reagent is prepared by mixing and dissolving 0.5 gm. of basic fuchsin in 100 cc. of 60 per cent ethanol to which has been added 10 cc. of concentrated hydrochloride water and 3 cc. of paraldehyde. The solution is placed overnight in the oven at 40 to 45°C. The deep purple solution is ready for use the following morning. When not in use, it is stored in the refrigerator.

Halmi's counterstain[13] is prepared by mixing and dissolving in 100 cc. of distilled water 0.2 gm. of Light Green, 1.0 gm. of Orange G, 0.5 gm. of Chromotrope 2R, 0.5 gm. of phosphotungstic acid, and 1.0 cc. of glacial acetic acid.

In addition to treating sections from all blocks of pancreases by the above method, additional ones were stained by Gomori's[14] procedure using chromium hematoxylin and phloxine, to demonstrate deposits of stainable glycogen.

Wilson's modification of Gomori's aldehyde-fuchsin technic stains the beta cell granules a deep purple and the background tissue pale green. Islets that contain beta cell granules stand out so clearly in these preparations (figures 1 and 2) that their total number in the sections can be counted rapidly with an automatic recorder. The area of the section was determined to the nearest square millimeter by placing it over squared paper. With the aid of a hand lens it was possible to exclude from area measurements regions of the section occupied by fatty or fibrous tissue. The number of islets was expressed in terms of square millimeters of sectioned pancreas. The *degree* of beta cell granulation in a representative number of islets was assessed from their examination under the higher magnifications of the microscope and expressed as one, two, three, or four plus. Examples of the two extremes of granulation (one plus and four plus) are shown in figures 3 and 4. An *index of beta cell granulation* (BCGI) was obtained by multi-

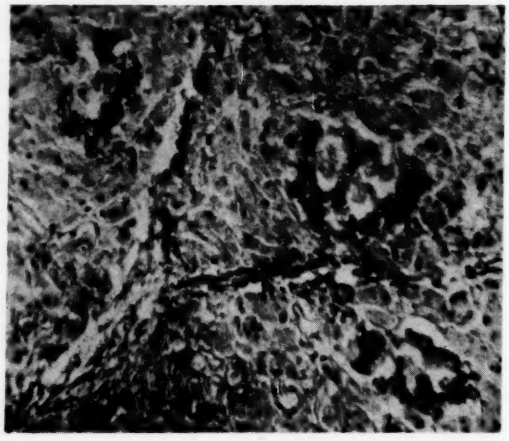

FIG. 1. Pancreas obtained at autopsy from a nondiabetic male patient; paraffin section stained by Wilson-Gomori aldehyde-fuchsin technic. Even under the low magnifications of the microscope, islets stand out clearly by virtue of their granules, which stain deep purple. X 100.

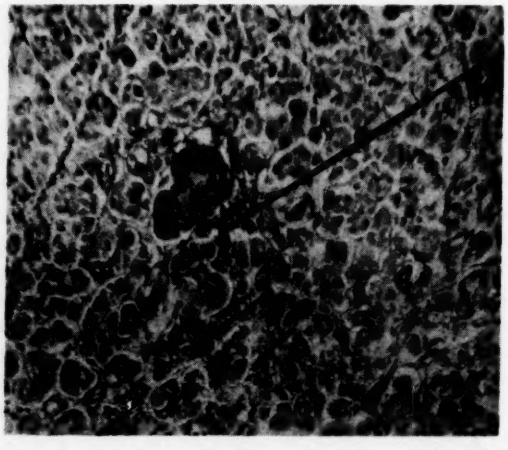

FIG. 2. Stain and magnification as for figure 1. The arrow points to a small islet in this pancreas obtained at autopsy from a diabetic patient. The islet stands out from the surrounding tissue because it contains a few beta granules.

FIG. 3. Oil-immersion field of an islet from section shown in figure 1. The intensely stained granules may be individually visualized under the microscope, although here they appear in the form of large dark clumps, due to the limitations of the photographic technic. X 1000.

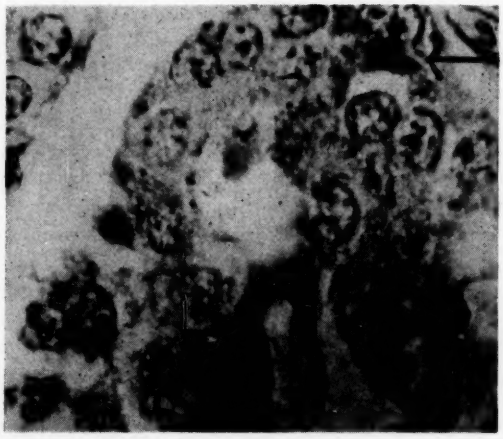

FIG. 4. Stain and magnification as for figure 3 in this oil-immersion field of a portion of the islet shown in figure 2 (diabetic). Only a few beta cell granules are present (arrow), but they can be clearly seen because of their deep staining by aldehyde-fuchsin.

plying the average number of islets per square millimeter of section-area by the estimated average degree of beta cell granulation (1, 2, 3 or 4) and dividing by ten. Both the BCGI and extractable insulin in units per gram of pancreas (I) are measures of their respective concentrations. All the histologic data were assembled before the observer (W.S.H.) was informed of either the case histories or the results of the insulin assays. Although these histologic methods are obviously far from quantitatively accurate, they correlated well with the amounts of insulin extracted from the same pancreases.

A total of 166 pancreases was subjected to these bioassays and histologic examinations. Eighty were obtained from diabetic adults and eighty-six from nondiabetic individuals coming to autopsy. The average interval elapsing between the time of death and fixation of the blocks of pancreas was between eight and nine hours (refrigerated). A control study of the effect of extensive autolysis on the index of beta cell granulation and extractable insulin in human pancreas was carried out and will be reported below.

RESULTS

The findings previously reported for many of the subjects in this series by Wrenshall, Bogoch and Ritchie[2] concerning the relationship of extractable insulin in pancreases of diabetic and nondiabetic adults to such factors as age, sex and body weight, are not altered by any of the data reported here. The present paper deals only with those aspects of the investigation concerned with comparisons of the intensity of beta cell granulation and extractable insulin in the 166 pancreases.

The graph in figure 5 illustrates the correlation of extractable insulin in units per gram of pancreas and the index of beta cell granulation (BCGI) for the entire

CORRELATION DIAGRAM: BETA-CELL GRANULATION VERSUS EXTRACTACTABLE INSULIN IN HUMAN PANCREAS: Nondiabetic, diabetic and unclassified subjects are indicated by open, filled and half-filled circles, respectively.

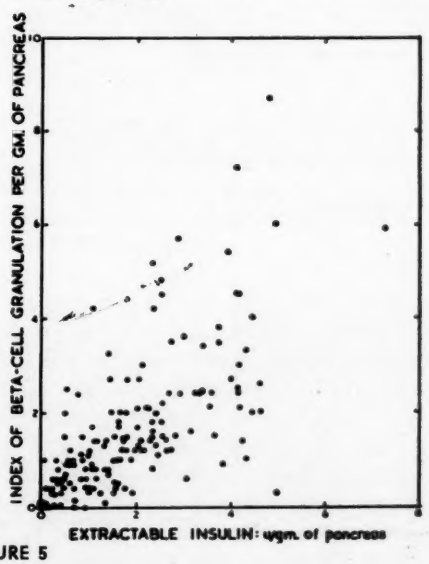

FIGURE 5

series of 166 pancreases. In figure 6 these data are presented separately for the nondiabetic and the diabetic subjects. Figure 7 similarly illustrates the correlation of extractable insulin (I) with islet frequency alone (rather than BCGI, for which islet frequency is weighed according to the intensity of beta granulation). A comparison of figures 6 and 7 reveals that the correlation of I with islet frequency alone is almost as good as that of I with BCGI in the *nondiabetic* subjects. But in the *diabetic* series, the correlation of I with BCGI is much better than that of I with islet frequency alone. The degree of beta cell granulation was therefore more uniform throughout the pancreases of the nondiabetic subjects than throughout those of the diabetics. Satisfactory correlations for the latter group could be obtained only when *both* the numbers of islets present in the sections and their average intensity of beta granulation (that is, BCGI) were taken into consideration in the computations. Mathematical analyses of the data provided the following information.

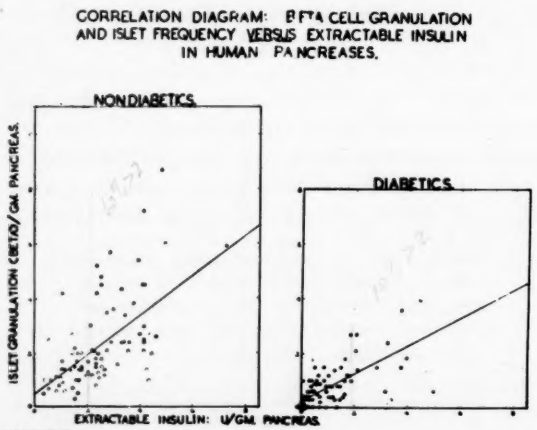

FIGURE 6

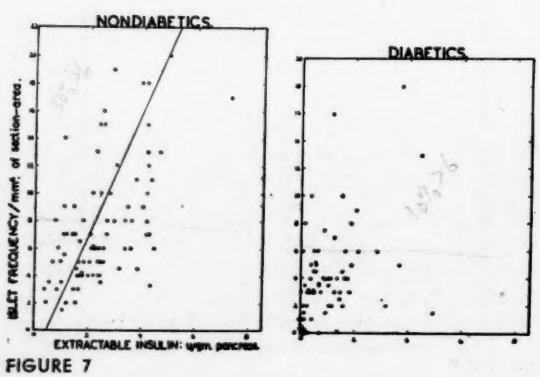

FIGURE 7

The equation of linear regression of BCGI on extractable insulin per gram of pancreas, (I), for 86 nondiabetic human subjects is:

$$BCGI = 0.510 + 0.719\ I.$$

The coefficient of linear correlation ($r \pm$ S.E.) between BCGI and I for the above is:

$$r = 0.584 \pm 0.072.$$

This coefficient differs very significantly from zero (p is far less than 10^{-10}).

The equation of linear regression of beta cell granulation (BCGI) on insulin extractable per gram of pancreas (I), for 80 diabetic adult human subjects is:

$$BCGI = 0.236 + 0.515\ I.$$

The coefficient of linear correlation, ($r \pm$ S.E.), between BCGI and I for the above 80 diabetic human subjects is:

$$r \pm S.E. = 0.680 \pm 0.0605.$$

This coefficient differs very significantly from zero (p is far far less than 10^{-10}).

The slopes of the straight lines of regression for nondiabetic and diabetic subjects differ significantly. The slopes and their standard errors are:

0.719 ± 0.0659 (BCGI/units insulin) for the 86 nondiabetics.

0.515 ± 0.0424 (BCGI/units insulin) for the 80 diabetics.

The difference is 0.204 ± 0.0766. The slope-difference is 2.64 times its standard error of estimate and is statistically significant at the 1 per cent level (that is, p=0.93 per cent and n is well over 30 so that p=t).

The possible interpretations that might be placed on these statistical findings are considered in the discussion.

Control Study of the Effect of Autolysis of Human Pancreas at 4°C on the Insulin Extractable Per Gram of Pancreas and the Index of Beta Cell Granulation

The dissected pancreas of a young, adult human male who was suddenly and accidentally killed was cut along its long axis in quadrants. Three of the strips were wrapped in cellophane and stored at 4°C. for periods of 1, 4 and 8 days. The remaining strip (control, zero days) was treated in the manner described under Methods for whole pancreases of the series. At the conclusion of their various periods of incubation, the remaining three strips were similarly processed. The results of the assays of extractable insulin (I) and computations of the indices of beta cell granulation (BCGI) are given in table I.

TABLE 1

Days of aging at 4°C	0	1	4	8
Index of beta cell granulation (BCGI)	2.4	1.8	1.4	1.2
Extractable insulin (I) units per gm. of pancreas	2.93	4.40	3.27	3.25

A downward trend is noted in the index of beta cell granulation (BCGI) but not in the extractable insulin of pancreas over the period of eight days. This trend might be interpreted to imply a passage of beta cell granular material into a soluble (histologically not demonstrable) form that presumably existed in the pancreas as physiologically active insulin. The longest period of aging of the pancreas in this experiment greatly exceeded the longest interval that elapsed between death and autopsy in any of the cases of the series of human subjects, either diabetic or nondiabetic. Any change in the ratio of BCGI to I within the first twenty-four hours elapsing after death would probably be overshadowed by biologic variation throughout the series. Evidence has already been presented (Wrenshall, Bogoch and Ritchie[2]) that biologic variation, rather than inaccuracies of measurement, constitutes the principal source of the large standard deviations which exist in determinations of extractable insulin of human pancreas. It is reasonable to assume that this conclusion might also be drawn for the estimations of the indices of beta granulation.

No reference will be made here to the frequency of various pathologic lesions such as islet fibrosis, hyalinization, and atrophy, encountered in the series. These findings are essentially the same for this extended series as for the original one that has already been reported (Hartroft[1]) and illustrated with photomicrographs in color.

DISCUSSION

Correlation of BCGI and I throughout both the diabetics and nondiabetics of the series is superior to that previously reported by one of us (Hartroft[1]) for 92 of the same pancreases comprising this series of 166 cases. Phase microscopy of sections stained by Bowie's[15] method was employed for visualization of beta granules in the initial study in 1950. Although this method clearly demonstrated granules under the oil-immersion objectives of the microscope, it did not permit practical estimations of either the numbers of islets present throughout the section or the average intensity of granulation in *all* the beta cells present. Reproducible rapid surveys under low magnifications of both total numbers of islets and the degree of granulation of all the beta cells are possible in sections of pancreas stained by the Wilson-Gomori aldehyde-fuchsin technic. The improved accuracy of the resulting estimates of beta granulation (BCGI) is demonstrated by the comparison of the previously reported coefficient of linear correlation of BCGI with I of 0.48 with the correlations reported here of 0.58 and 0.68.

Do the Granules of Beta Cells in Pancreases of Man Represent Insulin or Insulin Precursor?

Measurements of extractable insulin in pancreases of animals subjected to various experimental procedures such as injections of alloxan, glucose perfusion, treatment with diabetic extracts of the anterior pituitary, and so forth have shown good correlation with the presence or absence of beta cell granulation. The evidence that beta cells undergo degranulation or degeneration in experimental diabetes need not be reviewed here. There is, however, little in the available literature concerning the relation of extractable insulin and beta granulation in man.

Bell[10] correlated his survey of beta cell granulation in diabetic and nondiabetic human subjects with the assays of extractable insulin published by Wrenshall, Bogoch, and Ritchie[2] for their series. He concluded that a comparison of his histologic findings with their assays showed a fairly good correlation when the cases in the two series were compared for the various age groups. Thus, Wrenshall and associates found little extractable insulin in pancreases of diabetics under twenty years of age and Bell reported complete degranulation of beta cells in this group in his series. Correlation between the two series for other age groups was also fairly good.

The present paper affords a direct correlation between BCGI and I for 166 of the subjects in Wrenshall, Bogoch, and Ritchie's series. The results indicate that Bell's conclusions were warranted, even though they were based on data from two completely different series. There appears little doubt that beta granules do represent insulin or insulin precursor. But there are indications that insulin in the pancreas may be present in forms other than visible beta granules. It is entirely possible that under some circumstances granules may be present in appreciable numbers, but of a size too small to be resolved by the light-microscope; electron micrography is indicated here. But it is also possible that under still other conditions insulin might be present in some portions of the pancreas in a completely nongranular form. These possibilities provide theoretical explanations for those individual cases, most frequently encountered in the dia-

betic group, where the insulin assays were disproportionately higher than the estimates of beta granules. Taking the series as a whole, however, the equations of linear regression indicate clearly that a very nearly direct proportionality exists between the index of beta cell granulation and the amount of insulin extractable from the human pancreas. *This one-to-one relationship has been established beyond any possible statistical doubt for both nondiabetic and diabetic human pancreases.* It is the first positive evidence of an objective nature that the beta cell granules may represent or contain the stored insulin of human pancreas.

The slopes of the straight lines of regression of beta cell granules on extractable insulin per gram of pancreas differ significantly for adult diabetic and nondiabetic subjects. Less of the extractable insulin is present in the form of demonstrable beta granules in diabetic man than in nondiabetic cases. If the demands imposed on pancreatic insulin by hyperglycemia alone or by other metabolic or hormonal factors are greater in the diabetics than in the nondiabetics, insulin (beta) granules might be reduced to submicroscopic sizes or even altered to an entirely nongranular form. It seems reasonable to assume that insulin is carried in the blood stream in solution. Hence less of the extractable insulin in pancreas might be seen as beta granules under the light-microscope. If it were possible to repeat the experiments, using electron micrography in an extension of the morphologic studies, it is possible that the difference in the slopes of the two regression lines might be decreased or even entirely removed.

Applications to Clinical Pathology of Diabetes

The method of estimating the index of beta cell granulation was kept deliberately as simple as possible. Multiple blocks of tissue from single pancreases were avoided and sampling was restricted to one slice selected from the midportion of the gland. Technics of fixation, dehydration, imbedding, and sectioning of the tissue blocks are those in common use in many clinical laboratories. One of the objectives that Wilson achieved with his modification of Gomori's aldehyde-fuchsin stain was to shorten the length of time necessary to stain selectively the granules of the beta cells. His technic gives rapid, reproducible, and consistent results. So clearly do islets containing beta granules stand out in the sections under even the lower powers of the microscope that estimates of numbers of granules and granule-containing islets may be completed within a matter of minutes. We believe that clinical pathologists could quite easily estimate the index of beta cell granulation routinely in diabetic patients at autopsy. By extrapolation of the data presented here, estimates of extractable insulin in the pancreases thereby could be obtained without the necessity for the relatively elaborate facilities required for carrying out bio-assays. The accumulated data should prove of value to pathologists and clinicians under a number of circumstances.

The survey reported here does not consider other features of the islets such as alpha cell granules, ratios of alpha to beta cells, and so forth. The possible importance of additional data of this nature should not be minimized. Now that the relation between beta cell granules and pancreatic insulin in man has been established, these problems should be pursued.

SUMMARY

The extractable insulin of pancreases obtained at autopsy from 80 diabetic and 86 nondiabetic patients has been measured and expressed in units per gram of pancreas (I). These results have been correlated with estimates of the frequency and intensity of beta cell granulation (BCGI) for islets in histologic sections from midportions of the glands. Granules were easily visualized under the low powers of the microscope in sections stained by a modification of Gomori's aldehyde-fuchsin stain devised by Wilson. Statistical analyses of the results permitted the following conclusions to be drawn.

A nearly direct proportionality existed between the index of beta cell granulation (BCGI) and amount of insulin (I) extracted from unit weights of human pancreas. A one-to-one relationship was established between BCGI and I beyond any possible statistical doubt for both nondiabetic and diabetic human pancreases.

Less insulin per unit area of islets as well as smaller islet areas were demonstrated in the diabetic than in the nondiabetic pancreases.

The slopes of the straight lines of regression of beta cell granules on extractable insulin per gram of pancreas differed significantly for adult diabetic and nondiabetic subjects. It is concluded from this observation that less of the extractable insulin was present in the form of granules (demonstrable with the light-microscope) in the diabetic than in the nondiabetic subjects. This difference would be expected if a greater fraction of the insulin in pancreases of diabetics were present either as submicroscopic granules or in nongranular form than was the case for pancreases of nondiabetics.

Perhaps clinical pathologists may find that estimations of indices of beta cell granulation by the method described here are both feasible and useful. Our data would

enable them to interpret their indices in terms of extractable pancreatic insulin.

ACKNOWLEDGMENTS

The authors are grateful to Professor C. H. Best for his constant support and guidance throughout this project. They are indebted to Professors William Boyd and John Hamilton, Department of Pathology, University of Toronto, for providing access to autopsy material.

Mr. William Wilson willingly prepared the histologic material and Mrs. Margaret Cornell, Librarian in the Banting and Best Department of Medical Research, kindly aided in revision of the manuscript. The technical aid of Miss Isabelle Jasper and Miss Patricia Dolan in the extraction and assay of the insulin preparations is gratefully acknowledged.

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SUMMARIO IN INTERLINGUA

Correlation Inter le Granulation de Cellulas Beta e le Insulina Extrahibile del Pancreas

Esseva mesurate le insulina extrahibile ex le pancreases obtenite autopticamente ab 80 patientes diabetic e 86 patientes nondiabetic. Le resultatos esseva exprimite in unitates per gramma de pancreas e correlationate con estimationes del frequentia e del intensitate de granulation de cellulas beta in insulas in sectiones histologic ab portiones central del glandula. Le granulos esseva visibile sin difficultate sub le basse potentias del microscopio in sectiones colorate secundo le modification de Wilson del methodo a aldehydofuchsina de Gomori. Le analyse statistic del resultatos permitteva le sequente conclusiones.

Un quasi directe proportionalitate existeva inter le indice del granulation de cellulas beta e le quantitate de insulina extrahite ex unitates de peso de pancreas human. Isto esseva constatate ultra le possibilitate de dubita statistic in le caso tanto de nondiabetic como etiam de diabetic pancreases human.

In le pancreases diabetic — in comparation con le pancreases nondiabetic — minus insulina esseva constatate per unitate de area del insulas. Etiam le area del insulas esseva plus parve.

Il habeva un differentia significative inter adultos diabetic e nondiabetic in le inclination del lineas de regression del granulos de cellulas beta super le quantitate de insulina extrahibile per gramma de pancreas. Nos conclude ab iste observation que in diabeticos—comparate con nondiabeticos — minus insulina extrahibile esseva presente in le forma de granulos (demonstrabile per medio del microscopio conventional non-electronic). Iste differentia es plausibile si nos suppone que le pancreases de diabeticos — in comparation con le pancreases de nondiabeticos—contine un plus grande portion del insulina in le forma de granulos submicroscopic o in un forma nongranular.

Nos spera que pathologos clinic va trovar usabile e utile le methodo hic describite pro le estimation de indices del granulation de cellulas beta. Nostre datos permitterea a illes interpretar lor indices in re le extrahibile insulina pancreatic.

The Fate of Insulin in Altered Metabolic States

Neil J. Elgee, M.D., and Robert H. Williams, M.D., Seattle*

The insulin insufficiency of clinical diabetes mellitus and of experimental diabetes can be influenced quantitatively by many metabolic alterations. Ingle[1] has recently considered these relationships in a review of what he calls "heteropoietic" factors affecting carbohydrate metabolism. We have investigated the effects of some of these factors on the degradation of insulin labeled with radioactive iodine (insulin-I^{131}) in an attempt to elucidate their mechanism of action and to further the study of the metabolism of insulin.

METHODS

The radioactivity of insulin-I^{131} is essentially all protein-bound.† It has been found that after injection into a rat, this property is rapidly lost. A fraction of radioactivity appears that is not protein-bound, as measured by trichloracetic acid (TCA) precipitation, and thereby represents degradation of the insulin-I^{131}.

A standard procedure, fully described elsewhere,[2] has been adopted to measure this degradation and was used in these experiments.

In essence, there were two groups of rats of similar age, weight, and sex in each experiment. One, the experimental group, received a particular metabolic alteration, and the other group served as control. Both received a standard dietary preparation, and then all rats of both groups were given a standard dose of insulin-I^{131} intravenously. Fifteen minutes later the animals were sacrificed, and gastrocnemius muscle, blood, liver, and kidney removed. The radioactivity of these tissues was divided into a protein-bound fraction and a supernatant fraction by means of TCA precipitation. The concentration of radioactivity in these fractions was expressed as a ratio of the tissue concentration (per cent dose/gm.) to the initial total body concentration, to compensate for variations in body weight brought about by some of the metabolic alterations.

EXPERIMENTS AND RESULTS

In figure 1, the results of the experiments are summarized. The concentrations of radioactivity in the tissue fractions are shown as being either increased, decreased,

TCA SUPERNATANT = / TCA PRECIPITATE =	KIDNEY	LIVER	MUSCLE	BLOOD
INSULIN-I^{131} LOAD				↓ / ↑
INSULIN LOAD	↓ / ↓	↓ / ↑	↓ / –	↓ / ↑
HEPATECTOMY	– / –		↓ / ↑	– / ↑
NEPHRECTOMY		– / ↑	– / ↑	↓ / ↑
HYPOPHYSECTOMY	↓ / ↓	↓ / ↑	↓ / ↑	↓ / ↑
ADRENALECTOMY	– / –	– / –	– / –	– / ↓
GROWTH HORMONE	– / –	– / –	– / –	– / –
HYDROCORTISONE	– / –	↓ / –	– / –	– / –
GROWTH HORMONE and HYDROCORTISONE	– / –	↓ / ↓	– / –	– / –
THYROIDECTOMY	– / ↑	– / –	– / –	↓ / –
THYROXINE	– / –	↓ / ↓	↓ / –	↓ / –
TRIIODOTHYRONINE	↓ / ↓	↓ / ↓	– / –	– / ↓
GLUCOSE	↓ / ↓	– / –	– / –	– / –
FRUCTOSE	↓ / ↓	↓ / ↑	↑ / ↑	↓ / –
MC 2346	↓ / ↓	↓ / ↑	↓ / ↑	↓ / ↑

FIG. 1. The arrows indicate whether a particular metabolic state caused an increase, a decrease, or no change in the concentrations of radioactivity in the trichloracetic acid (TCA) precipitate and supernatant fractions of tissues measured fifteen minutes after intravenous insulin-I^{131}.

Presented at the Annual Meeting of the American Diabetes Association in San Francisco on June 20, 1954. The detailed data will appear subsequently in a series of publications.

From the Department of Medicine, University of Washington School of Medicine, Seattle.

Supported in part by grants-in-aid from the United States Public Health Service, the Atomic Energy Commission, and Initiative No. 171 of the State of Washington, and E. R. Squibb & Sons.

*Public Health Service Research Fellow of the National Heart Institute.

†The insulin-I^{131} was obtained from the Abbott Laboratories at Oak Ridge. In the preparation of the material, unbound I^{131} was removed by dialysis. Essentially all of the radioactivity remaining was precipitable upon the addition of trichloracetic acid.

or unchanged as compared with the control values for each experiment. In order to be charted as increased or decreased, differences had to have statistical significance of $p < .02$.

Insulin Loads

(A) *Insulin-I^{131}*. The experimental group was given a load of 222 *u*g. and the control group 2 *u*g. of insulin-I^{131}. With the load (222 *u*g.), there was proportionately less degradation as measured by blood levels. There was an increase in the fraction of the blood radioactivity in the TCA precipitate and a decrease in the fraction in the supernatant. This can be interpreted as showing that the degradation of insulin-I^{131} is rate-limited.

(B) *Insulin*. Of great significance is the fact that this same limitation of rate was found to result when both control and experimental groups received the same small (2-*u*g.) dose of insulin-I^{131}, but the experimental group received in addition, 220 *u*g. of nonlabeled insulin.* The nonlabeled insulin interfered with the degradation of the insulin-I^{131}; the TCA precipitable radioactivity was increased and the supernatant radioactivity was decreased, just as was the case with an insulin-I^{131} load. It would appear therefore that the system in which insulin-I^{131} is degraded does not distinguish between labeled and nonlabeled insulin. This gives weight to the supposition that the radioisotope technique gives information pertinent to the study of the metabolism of insulin.

Site of Insulin-I^{131} Degradation

When the liver was excluded from the circulation, there was an increase in the protein-bound radioactivity concentration in muscle and blood. Similar results were found in nephrectomized animals. Liver and kidney therefore are sites of insulin-I^{131} degradation. That they are not the only sites of this degradation, however, was shown in an experiment in which both hepatectomy and nephrectomy were done, and some degradation products still appeared in blood and muscle.

Adrenal and Pituitary Influences

Hypophysectomized animals showed decreased supernatant concentrations in all tissues and, conversely, increased protein-bound fractions in all except kidney. Degradation was therefore greatly diminished after hypophysectomy. Adrenalectomy, on the other hand, had very little effect, showing, if anything, some increased degradation as reflected in the blood. Growth hormone was completely without effect, and hydrocortisone reduced only the hepatic radioactivity. The combination of the two hormones had essentially the same effect as that of hydrocortisone alone.

Thyroid Function

After treatment with thyroxine or triiodothyronine, precipitable radioactivity in the tissues was decreased and, presumably, degradation was enhanced. Contrariwise, after thyroidectomy, degradation appeared to be diminished.

Glucose and Fructose Loads

Many experiments were done to assess the effects of these substances on insulin-I^{131} degradation. Large intravenous loads of either substance consistently lowered the renal radioactivity concentration. Other tissue fractions were not altered by glucose, but large doses of intravenous fructose resulted in greater concentrations of nonprecipitable radioactivity in muscle and liver, and lesser concentrations of supernatant radioactivity in liver and blood.

5-isopropylidene-2,4-dithiohydantoin (MC2346)†

This substance has been reported[3] to reduce the incidence of diabetes in rats after partial pancreatectomy. It was therefore given to rats to study its effect on insulin-I^{131} degradation. Pronounced changes resulted after either the intravenous or oral administration of MC2346. Precipitable radioactivity was increased, and supernatant radioactivity decreased, in liver, muscle, and blood, and both fractions of renal radioactivity were reduced. This picture then is essentially the same as that seen after hypophysectomy.

DISCUSSION

The evidence, presented in the insulin load study, is strong that the degradation system does not distinguish between labeled and nonlabeled insulin. Measurement of the rate of degradation of labeled insulin using the isotope method then may help to correlate the interrelation of nonlabeled insulin degradation and insulin sensitivity. Accordingly it is pertinent to consider the effects of metabolic alterations on insulin-I^{131} degradation with particular reference to changes in the biologic activity of insulin known to be brought about by such alterations.

In general, the results indicate that diminished insulin-I^{131} degradation was found in conditions of increased insulin sensitivity—for example, hypophysectomy—and, conversely, increased insulin-I^{131} degradation was found in conditions of relative insulin insensitivity; for example, in thyroxine-treated animals.

*Kindly supplied by Eli Lilly and Company.

†Kindly supplied by E. R. Squibb & Sons.

Therefore, although insulin is known to have an increased biologic action in hypophysectomized animals, yet, as these studies have shown, its degradation is reduced. On the other hand, Houssay[4] has produced insulin insufficiency by treatment with thyroid; our studies have shown that similar treatment (thyroxine or tri-iodothyronine) increases insulin-I^{131} degradation. Biologic activity would therefore, seem to be inversely related to degradation. This pattern was seen to a less pronounced degree in the thyroidectomized animals, who are insulin-sensitive in general and in whom degradation, in blood at least, was reduced.

Such a relationship strongly suggests that insulin degradation does not come about solely as the result of insulin action. It rather suggests that the process of degradation is closely connected with the inactivation of insulin. Many body tissues appear to take part in this degradation,[5] liver and kidney being active sites. That insulin-I^{131} concentrates in kidney has been considered suggestive that degradation represents inactivation, since no biologic function of insulin in kidney is known.[2] It is further of interest that with large glucose loads, renal insulin-I^{131} was decreased, and although insulin was in increased demand and was performing its physiologic action at an accelerated rate to metabolize the glucose, yet insulin-I^{131} degradation was unchanged. This also is consistent with the view that insulin-I^{131} degradation is not simply an accompaniment of insulin action. Fructose appeared to bring about decreased insulin degradation, but it is not known through what mechanism.

Since decreased insulin-I^{131} degradation seemed to be associated with increased physiologic insulin action, it seemed that it might be possible to inhibit insulin-I^{131} degradation as a therapeutic approach to diabetes mellitus. The relative insulin insufficiency of many of these patients might conceivably be relieved and physiologic balance restored, if it were possible to inhibit degradation of endogenous insulin. Many possible substances have been investigated, and of these, MC2346 has shown the most promise. It does inhibit the degradation of insulin-I^{131} and has been shown to reduce the incidence of diabetes after partial pancreatectomy. In the terms of the theories above, then, these two properties may be cause and effect. This substance therefore deserves further investigation.

SUMMARY

1. The process of degradation of insulin labeled with radioactive iodine (insulin-I^{131}) does not distinguish between labeled and nonlabeled hormone.

2. Insulin-I^{131} degradation takes place in many body tissues, notably in liver and kidney.

3. The degradation is reduced after hypophysectomy and probably after thyroidectomy. It is increased by thyroxine or triiodothyronine treatment. Growth hormone, hydrocortisone, and glucose have little effect on the degradation.

4. It is postulated that the degradation of insulin-I^{131} occurs in the process of inactivation of insulin, and if the degradation were to be inhibited the biologic activity of insulin might be enhanced.

5. A substance, MC2346, demonstrated such an inhibitory property, and the therapeutic implications of such a substance are discussed.

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DISCUSSION

GARFIELD G. DUNCAN, M.D., (*Philadelphia*): This important and well conceived study reported upon by Drs. Elgee and Williams is an application of the newest technics in the search to clarify obscure features in the metabolism of insulin.

The ready concentration of radioactivity in the kidney following the intravenous injection of insulin-I^{181} has been interpreted by the authors as indicating that the degradation of insulin in the kidneys is a major and not an incidental process and that the rate of degradation may be altered by influences known to affect the activity of insulin experimentally and clinically. These are new concepts of great potential importance.

The direction in which the studies have been undertaken makes it clear that these investigators fully realized that the tagged element might be a degradation product arriving in the kidney. Strong circumstantial evidences that this is not so have been presented. If this new concept is correct, it may provide another important step in the understanding of metabolic alterations surrounding the problem of diabetes. Comparisons of the behavior of

insulin-I^{131} with other labeled materials give strong support to the author's concept.

Clinically the alteration of the diabetes in patients with intercapillary glomerulosclerosis might represent a delay in the degradation of insulin permitting a more prolonged insulin effect in contrast with the effect in diabetic patients free from this disorder. Personally, I have looked upon the apparent decrease in the severity of the diabetes in these cases as being due largely to nutritional changes related to reduced caloric intake and reduced body weight. Admittedly, this has not been a completely satisfactory explanation of the amelioration of their diabetes.

Assuming that the conclusions arrived at by Drs. Elgee and Williams are correct — and it must be conceded that the evidence is very convincing — their findings might apply to the animal, or to the patient, receiving insulin either subcutaneously or intravenously in which cases the insulin reaches the systemic circulation by other than the portal circulation. It will be interesting to know if this tagged insulin injected into the portal vein, thereby following the same route as insulin in normal animals, follows the same distribution pattern or whether the greater collection of insulin-I^{131} will appear in the liver and less in the kidney. Possibly Dr. Elgee already has this information.

The cause or causes of diabetes are unknown. Damage to islet cell function leading to hyperglycemia and glycosuria probably is a late manifestation of a much more deep-seated process about which we know very little. An analogy of this concept is to be had in hemochromatosis in which diabetes is a relatively late manifestation of a disorder which happens to destroy pancreatic islets.

There are certain clues upon which the later onset of diabetes may be predicted with some certainty. Notable among these are the large babies of mothers long before diabetes becomes manifest. Disturbances in carbohydrate metabolism during pregnancy, the occasional appearance of retinal changes indistinguishable from diabetic retinitis, neuropathies, progressive atherosclerotic changes, changes in lipid metabolism, also may antedate the appearance of the signs upon which we pin the diagnosis of diabetes.

It is in the search for the fundamental fault which initiates these processess that such studies as reported by Dr. Elgee may prove most fruitful. He and Dr. Williams are delving into unexplored territory, and their ingenuity already has been rewarded.

Their further search into the mysteries surrounding the metabolism of insulin may well put a finger on the fundamental fault which instigates the series of abnormalities of which diabetes is but one. It is comforting to those of us who are primarily clinicians that this promising work holds no threat either to the destruction or removal or manipulation of the pituitary gland or of the adrenal gland.

FRANCIS D. W. LUKENS, M.D., (*Philadelphia*): I should like to know whether you have tested the rate of destruction after subcutaneous administration.

TOBY LEVITT, M.D., (*London, England*): This most fundamental and important work should help us understand many problems which have been worrying us for quite a long time. One little point which I did not get is, I believe adrenalectomy produced no change in the results, and I wonder why. Secondly, why was it necessary to give these big doses of insulin, and if these big insulin doses were given, could it be possible they affected the other endocrine systems indirectly. I should like to know why. Is it posssible to use other instrumental tools or methods to support these extremely important findings? Was this technic applied to animals or was it in part applied to human beings?

If possible, in their future work, I do hope the authors will be able to correlate the insulin function with the other hormones, especially the thyroid. They should really be complimented for most important work.

ARNOLD LAZAROW, M.D., (*Minneapolis*): Although the molecular weight of insulin in concentrated solution is in the neighborhood of 48,000, physical chemical studies have shown that in very dilute solution the insulin molecule dissociates into smaller units which have a molecular weight of 12,000 or possibly 6,000 units. Do you have evidence to show that the dissociated units of insulin are precipitated by trichloroacetic acid? Failure to precipitate the smaller insulin unit would certainly complicate the interpretation of your results.

FRANK L. ENGEL, M.D., (*Durham, N. C.*): I wonder whether you made any studies on the effect of diet on degradation of the insulin? Some years ago, Mirsky reported that the insulinase activity of the liver varied with the diet. Can you make any correlation between Mirsky's observation on liver insulinase and insulin degradation in your system?

NEIL J. ELGEE, M.D., (*Seattle*): All of our studies were done on rats in this particular investigative work. We have done some work with patients — for example, we have found diminished degradation in cirrhotics and in some patients with kidney disease. However, such

studies are still in the preliminary phase since we have been concerned primarily in the past year with insulin-I^{131} metabolism in the rat. Although we visualize that other tools are coming to be of value in this work, at the present time the study of degradation appears to be the most important.

We only used an insulin "load" in one of the experiments reported today. In the others each animal received less than one unit of insulin. The insulin "load" experiment purported to show the specificity of the labeled insulin — that it was not degraded in a different fashion from nonlabeled insulin — and in this experiment large doses were necessary. The animals were sacrificed 15 minutes after the dose. They did not appear ill, perhaps because of the high insulin resistance of the rat.

We have injected insulin-I^{131} into rats in the portal vein and compared distribution and degradation with that found after injection into the vena cava. After injection in the portal vein total radioactivity in liver was increased, and after vena cava injection renal total radioactivity was increased. However, the over-all degradation rate, that is, the relative concentration of tissue radioactivity in supernatant and precipitate fractions was no different. We were very interested in this experiment since work done by Weisberg and co-workers some years ago in dogs showed insulin to be less hypoglycemic when injected into the portal vein. They interpreted this to mean that the liver inactivated the material. We would not be at variance with their conclusions. We just did not demonstrate a similar effect using labeled insulin in rats. I hope to do the experiment in larger animals.

We have not studied the subcutaneous administration of insulin-I^{131}, Dr. Lukens. It could easily be done.

Adrenalectomy did not have any effect, it is true, on the degradation. I can simply say that as far as we could tell, degradation was not related to alterations in carbohydrate metabolism brought about by adrenalectomy.

As to the question of the TCA precipitability of diluted insulin, I think we have sufficient evidence that insulin does not get to a molecular size such that it is not precipitated by TCA, provided protein carrier is present. If carrier protein is not present precipitation may not be complete, but we have greatly diluted insulin-I^{131}, added a little plasma protein as carrier, and been able to precipitate the radioactivity completely.

As to the effects of diet, we have studied that, and the results conflict somewhat with Mirsky's work. He showed that the "insulinase" activity of liver from fasted rats was decreased if extracts or homogenate were used, but tended to be increased if slices were used. We fasted rats for three days, and we found the degradation of the labeled insulin to be somewhat reduced, a finding which fits in perhaps with observations in one of Mirsky's articles and not with the other.

ROBERT H. WILLIAMS, M.D., (*Seattle*): When we add equivalent small amounts of labeled insulin to boiled liver in one beaker and to surviving liver slices in another and permit the mixture to incubate for 15 minutes, we obtain approximately 100 per cent of radioactivity in the TCA precipitate of the boiled liver preparation, but considerably less in the precipitate of the surviving liver preparation. Therefore, the degree of dilution of the insulin would not account for the quantity not precipitated in the instance of the surviving liver slices, but it would be attributable to degradation of the insulin.

SUMMARIO IN INTERLINGUA

Degradation de Insulina in Alterate Statos Metabolic

1. Le systema in que insulina etiquettate a iodo radioactive (I^{131}) es degradate non distingue inter insulina etiquettate e non-etiquettate.

2. Le degradation de insulina a I^{131} occurre in multe texitos del corpore, specialmente in hepate e ren.

3. Le degradation es reducite post hypophysectomia e probabilemente post thyroidectomia. Illo es augmentate per le administration de thyroxina o triiodothyronina. Hormon de crescentia, hydrocortisona, e glucosa influe pauco super le degradation.

4. Nos postula que le degradation de insulina a I^{131} occurre in le processo de inactivation de insulina e que le inhibition del degradation es possibilemente un methodo pro augmentar le activitate biologic de insulina.

5. Un substantia que demonstrava le potentia de un tal inhibition es MC2346. Le implicationes therapeutic de iste facto es discutite.

Control of Diabetes and Other Features of Acromegaly Following Treatment with Estrogens

*E. Perry McCullagh, M.D., John C. Beck, M.D.,**
and C. A. Schaffenburg, M.D.,† Cleveland

In this article we report reversal of impaired carbohydrate tolerance and other favorable clinical and metabolic effects resulting from the administration of large doses of estrogen to six acromegalic patients.

Acromegaly is the most outstanding example of the relationship of growth hormone to human diabetes mellitus. The role of growth hormone in ordinary clinical diabetes is unknown. If future investigations demonstrate such a relationship, the control of defective glucose tolerance by means of pituitary inhibition will take on special importance.

Diabetes mellitus is a common accompaniment of acromegaly. Coggeshall and Root[1] in reviewing 153 cases of acromegaly, including 100 formerly reported by Davidoff and Cushing,[2] found glycosuria in 35 per cent and diabetes in 17 per cent. These authors considered diabetes to be present in those patients showing persistent glycosuria accompanied by hyperglycemia and abnormal glucose tolerance tests. They concluded that this diabetes does not differ clinically from diabetes mellitus.

The favorable effect of estrogens in experimental diabetes is not yet clearly understood. In 1933, Barnes, Regan and Nelson[3] reported the amelioration of pancreatic diabetes in dogs by the use of estrogens. Nelson and Overholser[4] extended these observations to monkeys and were able to show a reduction in the hyperglycemia and glycosuria of subtotally and totally depancreatized animals; this also occurred in animals made diabetic by anterior pituitary extracts. The authors postulated that the effect was mediated by suppression of the pituitary activity concerned with carbohydrate metabolism. More recently Foglia, Schuster and Rodriguez[5] and Rodriguez[6] have extended these observations to the partially depancreatized, force-fed rat treated with diethylstilbestrol. Following an initial aggravation of the glycosuria, the manifestations of diabetes gradually disappeared on continuous administration of the hormone. The effect was partly attributed to an estrogen suppression of anterior pituitary activity, although a direct action on the beta cells of the remaining pancreatic tissue, as well as on carbohydrate metabolism, was also postulated. Claims have been made that clinical diabetes mellitus may be ameliorated by the use of estrogens.[7-9] Such work needs to be extended before a critical evaluation can be made. Clinical improvement in various features of acromegaly has been reported. Changes have included symptomatic control,[10, 11] lowered creatinine excretion,[12] suppression of lactation,[13] and reduction in the abnormally high level of serum phosphorus.[14, 15]

The experiments of Houssay, Biasotti and Rietti[16] and of Evans and his associates[17] on the production of diabetes in experimental animals by the administration of growth-promoting pituitary extracts led to the belief that growth hormone and the diabetogenic principle of the anterior hypophysis are identical. On the other hand, Zondek[18] in 1936 produced inhibition of development and dwarfism in the rat and chick by means of estrogenic hormone administration. He believed that this inhibition was caused by a suppression of the gonadotropic and growth-promoting principles of the anterior lobe, since Evans' growth hormone caused a resumption of growth in these dwarfed animals. On the basis of their findings, the beneficial effects of estrogens in experimental diabetes might be explained by an inhibition of anterior pituitary growth hormone production. A direct antagonism between estrogens and growth hormone is not substantiated by the experiments of Young,[19] who was unable to show any beneficial effect from estrogen treatment in dogs made diabetic after temporary administration of growth hormone preparations.

A new problem is raised by the recent experiments of Raben and Westermeyer,[20] who have apparently dissociated the growth-promoting from the diabetogenic principle of the anterior hypophysis. These authors, by treating dogs with potent growth hormone prepared by

*Former Fellow in Endocrinology, Cleveland Clinic; present address, Royal Victoria Hospital, Montreal, Canada.

†Former Fellow in Research, Cleveland Clinic; present address, Research Dept., Mt. Sinai Hospital, Cleveland, Ohio.

From The Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute, Cleveland, Ohio.

a method developed by Astwood, failed to demonstrate glycosuria in their experimental animals, whereas other growth hormone preparations, obtained by a different process, readily caused glycosuria. The authors believe the diabetogenic principle to be a contaminant of the now available growth hormone extracts.*

The observations of Young[21, 22] and others mentioned previously[16, 17] on the production of diabetes in experimental animals by means of growth-promoting pituitary extracts suggest that in the acromegalic, diabetes is due to an excess production of these principles. The fact that a large percentage of acromegalic patients show no evidence of diabetes may indicate that the two possible principles involved in this disease (the diabetogenic and growth hormone) are not necessarily concomitantly elevated. The reversal of glucose tolerance in our cases by large doses of estrogens suggests an inhibition of the anterior pituitary activity concerned with carbohydrate metabolism as part of the mechanism, whatever the principles involved may be.

MATERIALS AND METHODS

Six patients with well-established acromegaly were repeatedly observed for months or years. One of these cases (case 2) has been briefly reported previously.[23] All the patients were white women, ranging in age from 24 to 54 years. The signs and symptoms of acromegaly had been present for from 1 to 16 years prior to this study.

Glucose tolerance tests, using a 100 gm. single oral dose, were carried out before treatment and at intervals during subsequent visits. The upper limits of normal for this test in our experience are as follows: fasting 100 mg. per 100 cc., one-half hour 170 mg.; one hour 170 mg.; two hours 130 mg.; three hours 110 mg.; and four hours 110 mg.

Four of these patients had diabetic glucose tolerance curves, and in the other two the glucose tolerance was mildly impaired. In addition, a fasting serum phosphorus and occasionally an alkaline phosphatase were obtained. Basal metabolic rate determinations were done when feasible. Hand volumes were measured by a water displacement technic, which, although not as accurate as anticipated, clearly demonstrated the trends in hand size. The patient's clinical status was carefully evaluated at each visit and other diagnostic procedures were employed as indicated.

All patients initially received stilbestrol in gradually increasing doses until a maintenance dose varying between 10 and 60 mg. daily was reached. The two patients who manifested intolerance to this drug were given ethinyl estradiol† in increasing doses, from 0.15 to 5.0 mg. daily. All these patients were treated as outpatients. Weighed or measured diets were not prescribed except in case 5, and no treatment for the diabetes except that listed was given. There were no conspicuous changes in body weight during the period of observation except in case 4, and in that instance it was striking that the blood sugar levels became lower while the patient became more obese. Nausea was not a problem that interfered with food intake in any except case 2, and here it was temporary, disappearing completely when ethinyl estradiol was substituted for stilbestrol. Body weights were not obtained at the time of each glucose tolerance test. Known weights of each patient showing the trend are given at the end of each case report.

The history, clinical and laboratory findings, and the course of the disease during estrogen administration for these six patients are as follows.

CASE REPORTS

Case 1. This patient first came to us in 1933 at the age of 34 years. Her complaints at that time centered about a gradual enlargement of her hands and feet with alteration of her features, which had been observed for eight months. Physical examination revealed early acromegalic traits and a blood pressure of 155/90. Laboratory examinations showed a faint trace of albumin in the urine, hemoglobin 91 per cent, and white cell count 7450. Wassermann and Kahn reactions were negative, and the blood sugar five hours after eating was 132 mg. per 100 milliliters. A roentgenogram of the skull showed enlargement of the sella turcica. The visual fields were normal for form and color. The glucose tolerance curve was as follows: fasting 111 mg. per 100 cc.; one-half hour 179; one hour 178; two hours 152; and three hours 105.

The patient has been periodically examined since her initial visit and a slow progression of the acromegaly has been observed. Amenorrhea occurred in 1934; at that time the blood pressure was 140/100. She received several courses of x-ray therapy to the pituitary, with

*F. G. Young (personal communication) doubts the dissociation of growth and diabetogenic factors. He believes that the apparent dissociation is best explained on the basis of the lower concentration of growth hormone in the extracts prepared by Raben and Westermeyer, as well as the fact that these extracts were used in solutions of low *p*H.

†Estinyl supplied through the courtesy of Dr. E. Henderson of the Schering Corporation.

apparent temporary arrest of the disease. In 1940, 1941, and 1942 the disease was seemingly quiescent and the only complaints were excessive perspiration and hot flashes. Pelvic examination revealed pronounced uterine atrophy; and a vaginal smear showed estrogen deficiency, which led to the institution of stilbestrol therapy, 1 mg. per day for three weeks in each month, in an attempt to control what were believed to be menopausal symptoms. Little relief was obtained and the medication was taken intermittently. It was increased to 3 mg. per day.

In 1948 the patient had a complete clinical and laboratory re-evaluation. Physical examination revealed typical acromegalic features. The blood pressure was 160/112. Roentgenograms of the sella turcica were unchanged. The visual fields remained normal. The serum calcium was 11.4 mg. per 100 cc. and the serum phosphorus 4.6 mg. The basal metabolic rate was plus 10 per cent and the plasma cholesterol 164 mg. per 100 cc. The glucose tolerance curve again revealed impairment; it was, fasting 98 mg. per 100 cc.; one-half hour 134; one hour 161; two hours 185; and three hours 171. Urinary gonadotropins were less than 6.6 mouse units per 24 hours. It was believed at this time that the acromegaly was in a more active phase; consequently the stilbestrol dosage was gradually increased over a five-month period to 10 mg. daily. At the end of this time the glucose tolerance curve had returned to normal. This reversal and a fall in the serum phosphorus to between 2.1 and 3.0 mg. per 100 cc. were associated with clinical improvement. The basal metabolic rate remained in the region of minus 2 per cent to plus 5 per cent.

From 1948 to 1950 a curious group of neurologic symptoms developed, consisting of staggering gait, mental sluggishness, and slurring and monosyllabic speech. There was some ataxia, rotary nystagmus, hyperreflexia, and a positive Babinski test on the right. It was believed that there was a low-grade bilateral cerebellar defect, perhaps due to demyelination, which is occasionally present in long-standing acromegaly. These phenomena had not altered appreciably when the patient was last seen in April 1951. Stilbestrol, 10 mg. daily, had been continued and the acromegalic process did not seem to have made further progress. The blood pressure had remained at an average of 150/100. The last glucose tolerance curve, in April 1951, was normal except for the three-hour level, which was slightly elevated; it was fasting 79 mg. per 100 cc.; one-half hour 109; one hour 147; two hours 127; three hours 116; and four hours 98. The serum phosphorus was 3.3 mg. per 100 cc.

The results of the glucose tolerance tests are charted in figure 1. The body weight at the time of the first test was 189½ pounds and at the time of the second test it was 189 pounds. No weight was recorded at the time of the third test, but one year later the body weight was 186 pounds.

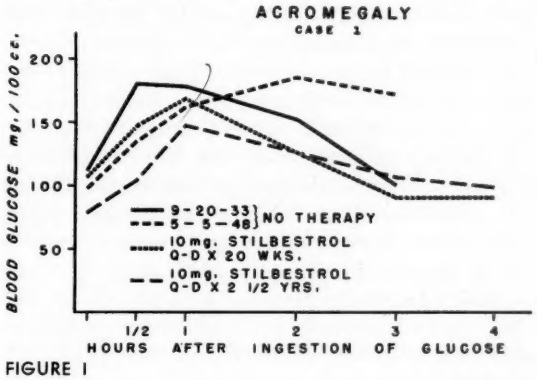

FIGURE 1

Case 2 (previously reported[23]). A 45-year-old woman was referred because of prolapse of the uterus and acromegaly. Coarsening of the facial features, enlargement of the hands and feet, and moderate growth of hair on the arms and legs had been progressing for at least eight years. Amenorrhea had occurred abruptly six years previously. There was severe daily headache and backache. Three weeks prior to examination, arterial hypertension was discovered. The family and personal histories were noncontributory.

Physical examination revealed the features associated with severe acromegaly, including a dorsal kyphosis which prevented the patient from lying supine. There was moderate hypertrichosis and acne over the face and chin. The thyroid was slightly enlarged. The heart was enlarged to the left. The blood pressure was 194/130. There was a marked uterine prolapse.

Laboratory examinations were as follows: The urine had a specific gravity of 1012 to 1020, with a trace of albumin on several examinations. The hemoglobin, white cell count, blood sugar, and blood urea were normal. Wassermann and Kahn reactions were negative. The serum phosphorus was 4.3 mg. per 100 cc., the serum calcium 11.5 mg., and the alkaline phosphatase 6.1 Bodansky units. The basal metabolic rate was plus 51 per cent and the serum cholesterol was 187 mg. per 100 cc. The uptake of radioactive iodine was 8 per cent at the end of two hours. The glucose tolerance curve was definitely abnormal. The urinary gonadotropins were

less than 13 and more than 6.6 mouse units per 24 hours on consecutive examinations. X-ray examination of the sella turcica showed great enlargement with depression of the floor, and thinning of the dorsum sellae and posterior clinoid processes. There were abnormally prominent frontal sinuses, hyperaeration of other sinuses, and prognathism. Roentgenographic examination of the hands showed tufting of the terminal phalanges. The visual fields were normal for form and color.

Stilbestrol therapy, 1 mg. daily increasing to 2 mg. daily, was initiated but after one month was discontinued because of severe nausea. Ethinyl estradiol was begun with a dosage of 0.04 mg. per day, increased gradually to 1 mg. per day and continued for three months. During this period the severe headache and backache disappeared, the coarseness of features decreased, and the size of the nose, hands, and feet diminished.

Hand volumes after treatment were left 450 cc. and right 485 cc. Discontinuance of therapy for two months resulted in an increase of hand volume (left 515 cc. and right 550 cc.), a return of occipital headache and backache, and re-enlargement of the nose, lips, and tongue.

One milligram of ethinyl estradiol daily was resumed for a nine-month period, after which the dosage was increased to 2 mg. daily for the next year. Treatment was then discontinued. During therapy there occurred a complete subsidence of symptoms and a noticeable increase in strength; the patient's rings became loose, her thimbles fit her fingers for the first time since the onset of her illness, and fine movements again became possible. Excessive perspiration ceased. No alteration in blood pressure occurred. Changes in hand volume are recorded in table 1.

After four months without therapy the patient was re-examined. Symptoms had returned as on the previous cessation of estrogen administration. Alterations which occurred in the glucose tolerance, serum phosphorus, alkaline phosphatase levels, and basal metabolic rate are demonstrated in figures 2 and 3.

Shortly after cessation of estrogenic therapy the patient developed a mild cerebrovascular accident from which she gradually recovered. At this time she first noticed blurring of vision, especially laterally, and repeated examinations of the visual fields showed a progressive development of a bitemporal hemianopsia. Because of this development and the return of active acromegaly, the use of ethinyl estradiol was resumed in a dosage of 2 mg. daily. However, since no immediate improvement in the visual fields occurred, the patient received a course of x-ray therapy directed to the pituit-

TABLE 1
Changes in hand volume. Case 2.

Date	Therapy	Hand Volumes R.	L.
8-6-48	Ethinyl estradiol 1 mg./day for 13 weeks	485 cc.	450 cc.
8-26-48	No therapy for 20 days	500 cc.	485 cc.
9-30-48	No therapy for 53 days	550 cc.	515 cc.
7-28-50	Ethinyl estradiol 1 mg./day 2 mg./day for 52 weeks	525 cc.	438 cc.
11-9-50	No therapy for 10 weeks	545 cc.	520 cc.

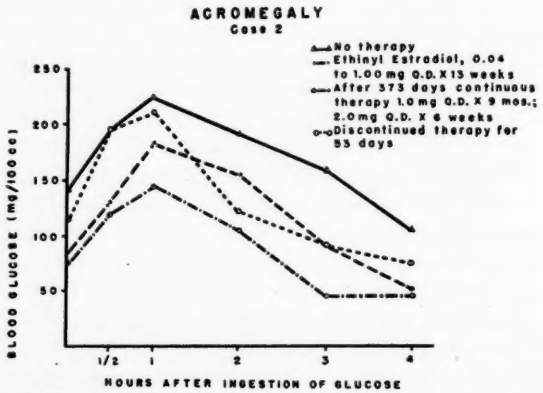

FIGURE 2

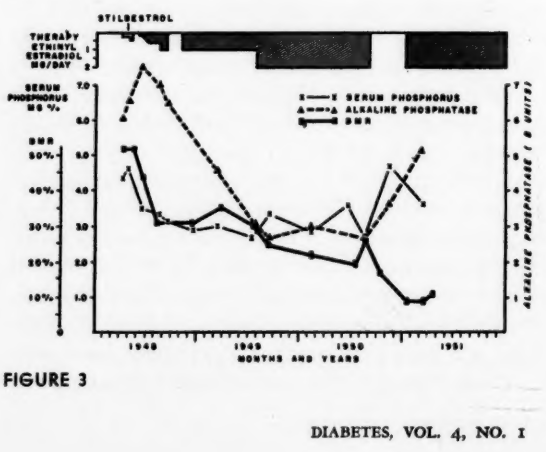

FIGURE 3

ary, calculated to deliver approximately 2000 roentgen units to the gland. This produced no additional effect. With continued estrogenic therapy there has been slow progressive improvement. When last seen after 11 months of continuous treatment the patient felt greatly improved, more so than for many years. Arterial hypertension, however, had not diminished. The average blood pressure was 210/120. The body weight at the time of the first glucose tolerance test was 137 pounds and at the time of the last test was 150 pounds.

Case 3. This patient was referred by her physician at the age of 45 years because of a questionable lesion of the cervix discovered on a routine examination. The family and past histories were noncontributory except for a long series of injections for a "blood condition" which she was said to have had since birth.

Physical examination revealed a slight coarsening of the features, which to one observer suggested myxedema, and a large friable mass on the posterior lip of the cervix which bled freely when touched.

Laboratory examinations were as follows. Urinalysis was normal. The red cell count was, 4,000,000; the hemoglobin 8.8 gm.; and the white cell count 7800. The blood sugar was normal. The basal metabolic rate was plus 17 per cent and the serum cholesterol was 207 mg. per 100 cc. Wassermann and Kahn reactions were 4 plus.* X-ray examination of the chest was normal except for possible enlargement of the left ventricle. A cervical biopsy showed a moderately well-differentiated squamous cell carcinoma.

Admission to the hospital was recommended and two separate cervical applications of radium were given, totaling 3468 mg. hours. At that time the serum phosphorus was 4.2 mg. per 100 cc. and roentgenograms of the skull showed features suggestive of acromegaly with enlargement of the sella turcica, depression of the sellar floor, and thinning of the anterior clinoid processes. Since no symptoms were present, little attention was paid to these findings for two years; the patient then noticed swelling of her face, particularly the eyelids. There had been progressive enlargement of the hands and feet. The blood pressure was 150/100. X-ray examination of the chest was normal. Skull films showed enlargement of the sella turcica, but no appreciable change since the previous examinations. The visual fields were normal. The serum phosphorus was 4.3 mg. per 100 cc. The glucose tolerance curve was compatible with diabetes mellitus. The basal metabolic rate was plus 4 per cent. Hand volumes were right 470 cc. and left 445 cc.

Treatment with stilbestrol, 10 mg. daily, was begun. Six weeks later the serum phosphorus had fallen to 3.4 mg. per 100 cc. and the glucose tolerance had improved. Five months after initiation of therapy there had been improvement in her acromegaly and a decrease in the size of the nose, hands, feet, ankles, and ears. Stilbestrol was discontinued for a time, but when her abnormal features became worse stilbestrol, 20 mg. daily, was resumed. Six weeks later she felt that a reduction in her abnormal features had occurred. Hand volumes tended to substantiate this; they were right 435 cc. and left 410 cc. The serum phosphorus had fallen to 3.0 mg. per 100 cc. The glucose tolerance curve, however, remained impaired. The stilbestrol dosage was increased to 40 mg. daily. When the glucose tolerance test was repeated after four weeks of this increased dosage no alteration had occurred, although clinically the patient was much improved. The serum phosphorus was 2.6 mg. per 100 cc. The stilbestrol dosage was increased to 60 mg. daily for three months, at the end of which time the glucose tolerance curve was fasting 88 mg. per 100 cc.; one-half hour 143; one hour 162; two hours 176; three hours 113; and four hours 75. The serum phosphorus was 2.9 mg. per 100 cc., the calcium 9.8 mg., and the cholesterol 248 mg. The basal metabolic rate was plus 8 per cent. The uptake of radioactive iodine was 35 per cent at the end of 48 hours, with a conversion ratio of less than 10 per cent. The hand volumes were right 468 cc. and left 443 cc. The patient continued to take 60 mg. of stilbestrol per day, and two months later the glucose tolerance curve was fasting 85 mg. per 100 cc., one-half hour 157; one hour 177; two hours 187; three hours 79; and four hours 53. The serum calcium was 10.0 mg., and the serum phosphorus was 3.3 mg.

The results of the glucose tolerance tests are charted in figures 4 and 5. The body weight at the time of the first glucose tolerance test was 150 pounds and at the time of the last test it was 169 pounds.

Case 4. A 24-year-old woman was referred because of amenorrhea of three years duration, enlargement of the hands and feet, and coarsening of the features over a two-year period. Her physician had treated her with a thyroid-pituitary preparation, followed by x-ray therapy to the pituitary totaling 6000 r., all without noticeable benefit. The family and past histories were noncontributory.

Physical examination revealed an obese woman weigh-

*Spinal fluid examinations were entirely normal, and it was believed that the syphilis was probably congenital and that it had been adequately treated.

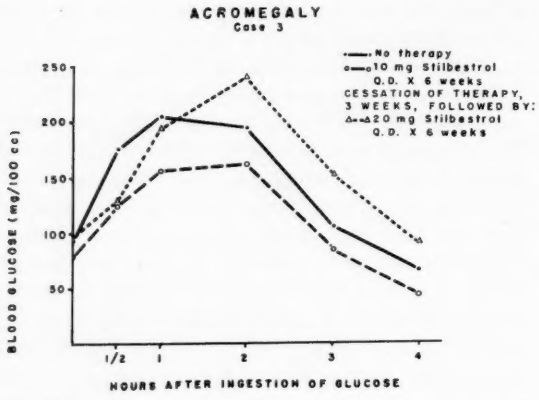

FIGURE 4

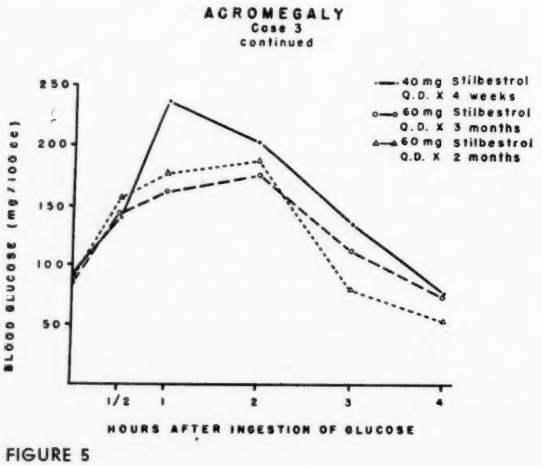

FIGURE 5

stilbestrol, 20 mg. daily, was administered. When the patient was seen two months later, dramatic improvement was evident and she felt better than at any time in the previous two years. The coarseness of her features had decreased. The nose, lips, tongue, and hands were smaller. The hand volumes were right 492 cc. and left 510 cc. The serum phosphorus had fallen to 2.9 mg. per 100 cc. and the glucose tolerance curve remained unchanged. Five and one-half months after beginning therapy she remained well. The serum phosphorus was 3.3 mg., and the glucose tolerance was increased, the curve lying well within normal range. It is of interest that the one-hour blood sugar had fallen from 192 to 145 mg. per 100 cc. in spite of a 17-pound gain in weight. Stilbestrol therapy is being continued.

Effects on glucose tolerance are demonstrated in figure 6. The body weight at the time of the three tests was 230, 245, and 247 pounds.

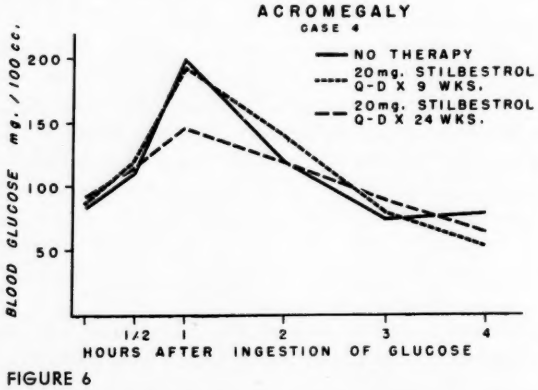

FIGURE 6

ing 230 pounds with typical acromegalic features. Laboratory examinations including urinalysis, hemoglobin, white cell count, fasting blood sugar, and Wassermann and Kahn reactions were normal: The serum phosphorus was 5 mg. per 100 cc., and the glucose tolerance curve was mildly impaired. Roentgenograms of the skull showed the usual acromegalic changes with definite destruction of the sella turcica. The visual fields were normal. The basal metabolic rate was plus 4 per cent and the uptake of radioactive iodine at the end of 22 hours was 12 per cent. The urinary gonadotropins were more than 13 and less than 105 mouse units per 24 hours. An endometrial biopsy revealed a proliferative phase judged to be about the third day of a classic 28-day cycle. The hand volumes were right 530 cc. and left 526 cc.

A diagnosis of active acromegaly was made and

Case 5. A 59-year-old woman appeared at the Clinic complaining of enlargement of the hands and feet and a change in her features over the past ten years. She had been having headaches increasing in severity during the preceding five years. In addition she had noticed palpitation, dyspnea on exertion, and excessive nervousness for the past one and one-half years. Four years previously she had had similar symptoms and an elevated basal metabolic rate. A diagnosis of "toxic goiter" had been made and thyroidectomy performed. The family and past histories were noncontributory.

At physical examination the patient had typical acromegalic features. She was stocky and well nourished. The blood pressure was 190/120. Laboratory examinations, including urinalysis, hemoglobin, white cell count, fasting blood sugar, and Wassermann and Kahn reactions, were normal. The basal metabolic rate was plus

31 per cent and the plasma cholesterol 323 mg. per 100 cc. The uptake of radioactive iodine was 30 per cent in 27 hours. The serum phosphorus was 3.4 mg. per 100 cc.

On x-ray examination the sella turcica measured 14 by 14 mm. and the floor was depressed. A chest film revealed no abnormality. The visual fields were normal for form and color. Glucose tolerance curves were diabetic in type.

The patient was placed on a diet consisting of 160 gm. of carhohydrate, 100 gm. of protein, and 107 gm. of fat, totaling 2003 calories. Also an attempt was made to evaluate the effects of propyl-thiouracil, 500 mg. daily, on the hypermetabolism of acromegaly. This dosage was continued for three months without subjective or clinical improvement. The basal metabolic rate at the end of this course of therapy was plus 21 per cent, with no alteration in the glucose tolerance curve. Because of this lack of response to antithyroid drugs and an uptake of radioactive iodine of only 12 per cent, it was concluded that the hypermetabolism was of nonthyroid origin.

Stilbestrol, 20 mg. daily, was administered and within six months the patient showed distinct improvement. Her symptoms disappeared and there was a definite increase in strength. The serum phosphorus was 2.4 mg. per 100 cc., the basal metabolic rate plus 43 per cent, and the serum cholesterol was 250 mg. Glucose tolerance was improved but not yet normal. The uptake of radioactive iodine was 35 per cent.

Estrogen therapy was changed to ethinyl estradiol, 2 mg. daily, because stilbestrol appeared to have impaired the patient's appetite.

When this patient was seen again one year later she felt well. Her hands and feet were smaller and moved more freely, and her only complaint was a poor appetite. The glucose tolerance was much improved and the serum phosphorus was 3.4 mg. per 100 cc. The visual fields remained normal. The basal metabolic rate was plus 38 per cent and the plasma cholesterol 296 mg. per 100 cc. Therapy was continued as before. The blood pressure remained elevated at 180/130.

The changes in glucose tolerance are charted in figure 7. The body weight at the time of the first and last tests was 137 pounds.

Case 6. A 48-year-old woman sought medical attention because of progressive enlargement of the hands and feet with pain and numbness for seven years. She first noticed this condition when she was unable to replace her rings. Progression had been more rapid in the last

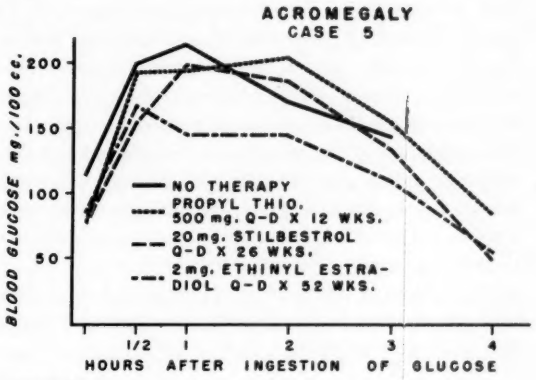

FIGURE 7

four years and had been accompanied by the gradual development of hoarseness. The past and family histories were noncontributory.

Physical examination revealed the typical early changes of acromegaly; the face, hands, and feet showed striking alteration when compared to a photograph taken five years previously. The blood pressure was 150/102, with no cardiac enlargement. The urinalysis, white cell count, hemoglobin, Wassermann and Kahn reactions were normal. The fasting blood sugar was 113 mg. per 100 cc.

X-ray examination of the sella turcica revealed enlargement with thinning of the walls and floor. The serum phosphorus was 4.0 mg. per 100 cc. The alkaline phosphatase was 2.3 Bodansky units. The basal metabolic rate was minus 1 per cent. The glucose tolerance test was impaired, the one-hour level being 243 mg. per 100 cc. The urinary gonadotropins were more than 318 mouse units per 24 hours. Hand volumes were right 510 cc. and left 495 cc.

Stilbestrol, 20 mg. daily, was given, and when the patient was seen three weeks later her features were less coarse and her lips, tongue, hands, and feet were smaller. Also her limbs were more flexible, and the pain was reduced in severity. Hand volumes were right 480 cc. and left 490 cc.

Seven weeks after initiation of this therapy the glucose tolerance curve was normal and pain in the extremities had disappeared; however, a few days later pain in the hands reappeared and the stilbestrol dosage was increased to 30 mg. per day. The blood pressure at this time was 204/110. A low-sodium diet was instituted, with some beneficial results, and four months afterward the blood pressure was 188/100. Pain in the hands persisted and there was transient swelling. A glucose toler-

ance test after 22 weeks of continuous therapy with 30 mg. of stilbestrol daily showed the following values: fasting 104 mg. per 100 cc.; one-half hour 177; one hour 236; two hours 187; three hours 98; and four hours 75. The stilbestrol dosage was increased to 50 mg. daily and at the end of five weeks of this therapy the glucose tolerance values were fasting 88; one-half hour 178; one hour 178; two hours 161; three hours 65; and four hours 62. The blood pressure was 170/95, and the patient reported pronounced improvement.

The results of the glucose tolerance tests are given in figure 8. The body weight at the time of the first test was 124 pounds; two months after the last test it was 137 pounds.

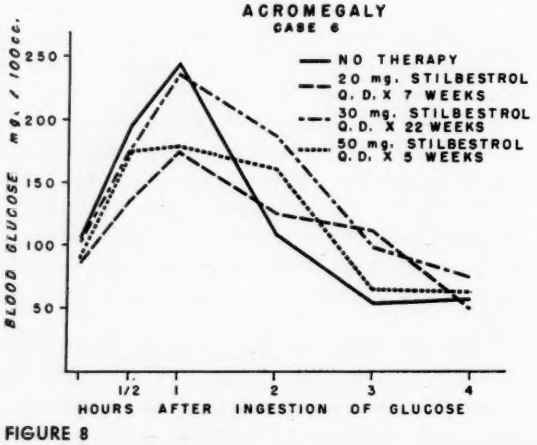

FIGURE 8

OVER-ALL RESULTS

All pertinent observations for this group of patients are summarized in table 2. These six patients had abnormal glucose tolerance curves, and all showed a reversal to normal or almost normal limits while receiving either stilbestrol or ethinyl estradiol. In one patient (case 3) this effect could not be reproduced following a period of cessation of estrogen administration, although later tests after more intensive therapy showed curves well within the normal range.

All patients showed a significant and sustained fall in fasting serum phosphorus levels. Alkaline phosphatase determinations were done in only two cases; in one of them, after an initial rise, it dropped to normal levels.

Three patients had an elevated metabolic rate and a normal uptake of radioactive iodine. In only one of these did the metabolic rate fall to normal limits, and this after more than two years of treatment.

TABLE 2

Pertinent changes in six cases of acromegaly after treatment with estrogens*

Case	Age & Sex	Estrogen & Dose	Glu. Tol.	Ser. Phos.	Alk. P'tase	B.M.R.	Hand Vol.
1	49-F	Stilbestrol 10 mg./day	↑	↓	N.O.	N.C.	N.O.
2	45-F	Ethinyl Estradiol 1; 2 mg./day	↑	↓	↓	↓	↓
3	45-F	Stilbestrol 10; 20; 40; 60; mg./day	↑ ↓	↓	N.O.	N.C.	↓
4	24-F	Stilbestrol 20 mg./day	↑ ?	↓	N.O.	N.C.	↓
5	59-F	Stilbestrol 20 mg./day Ethinyl Estradiol 2 mg./day	↑	↓	N.O.	N.C.	N.O.
6	48-F	Stilbestrol 20 mg./day	↑	↓	N.C.	N.O.	↓

*Clinical status improved in all cases
N.O.—no observation N.C.—no change

Hand volumes were observed periodically in four cases, and all showed a definite decrease (as measured by a water displacement technic) during estrogen administration, which confirmed the observations of the patients.

There was definite clinical improvement in all cases, as manifested by relief of headache, when this was present, amelioration of pain in the extremities and back, and a decrease in sweating and hot flashes. All the patients noted a decrease in the coarseness of their features and diminution in the size of the ears, lips, and tongue. It is interesting that no effect on the elevated blood pressure was noted during the period of observation.

Clinical improvement was rapid and was usually noticeable within a few days, always within one week. Maximum benefit, however, took several months to become apparent. The earliest time for laboratory evidence of improvement was two weeks, but no conclusive information can be drawn from this series since all the patients were studied on an outpatient basis.

Both clinical and metabolic relapse occurred on cessation of estrogen administration, in approximately the

same time as the initial improvement had become apparent. In 3 cases (cases 2, 3, and 6) the glucose tolerance curve again became abnormal, requiring more intensive therapy to obtain a further response. This probably indicates not only that the effect is not a permanent one, but also that unresponsiveness to estrogens gradually develops, requiring a further increase in dosage. In case 2 the final period of treatment described included x-ray as well as estrogen, making it impossible to evaluate the effect of either of them fully. Attention is called to the fact that in this patient the glucose tolerance had previously become normal and after withdrawal of estrogen had again risen to diabetic range. This appeared to indicate that the estrogen therapy was having an effect and that the improvement in glucose tolerance was not due to gradual reduction in the activity of the acromegaly.

The serum phosphorus rose promptly on cessation of therapy and fell to previous levels when treatment was reinstituted. This also occurred in the one instance (case 3) in which reversal of the diabetic glucose tolerance curve could not be duplicated on one occasion, although the patient showed the previous clinical benefit. This apparent dissociation is interesting.

The complications of estrogen administration were anorexia, nausea, and abdominal complaints. These were troublesome in only one case (case 2); anorexia in a second case (case 5) led to the administration of ethinyl estradiol instead of stilbestrol, and although nausea was somewhat relieved the lack of appetite persisted.

Abnormal menstrual bleeding must be considered to have occurred in one patient (case 3), who after five months of treatment developed lower abdominal pain, due to hematometra which had developed because of a post-radiation cervical stenosis.

All patients experienced fullness and occasional sensitiveness of the breasts, together with a darkening of the areolae in those receiving stilbestrol, but in none were these findings troublesome.

In case 2 impairment of lateral vision developed after cessation of estrogen administration for ten months. Repeated visual field examination showed the progressive development of a bitemporal hemianopsia, and since no immediate improvement occurred after resumption of estrogen therapy, a course of x-ray treatment was given, without any additive effect. Pituitary surgery was not prescribed because of the poor cardiovascular status. On continuous ethinyl estradiol therapy there had been a slow progressive improvement in most features except the blood pressure.

DISCUSSION

We believe that the reversal of the abnormal glucose tolerance in acromegaly during estrogen administration is further evidence of a potent hormonal inhibition of the pituitary such as has been demonstrated by others.[10-15] Whether this improvement in carbohydrate metabolism is due to an inhibition of growth hormone or some other pituitary factor is still a matter of conjecture. Houssay[24] and others[5, 6] have suggested another possible mechanism, by demonstrating that estrogens decrease the incidence of diabetes in rats following subtotal pancreatectomy. This presumably is mediated through a stimulating action on the islands of Langerhans, which show hypertrophy and hyperplasia, especially of the beta cells. Barnes,[3] on the other hand, has shown an attenuation of diabetes in totally pancreatectomized dogs and monkeys on estrogen therapy.

One other possible mechanism exists, namely the peripheral action of estrogens on carbohydrate metabolism, which is as yet little understood.

The fall in serum phosphorus during estrogen administration is similar to that described by Reifenstein, Kinsell and Albright[14] and Kinsell and associates.[15] They demonstrated that an elevated serum phosphorus was associated with growth hormone activity in prepuberal growth, whereas when puberal growth occurred the serum phosphorus fell promptly, presumably owing to a steroid depression. Thus the serum phosphorus is a good index of growth hormone activity. Kinsell and associates[15] showed by assay that there was a fall in growth hormone activity of the serum in gigantism and acromegaly following androgen and estrogen administration. These observations, however, must be corroborated when better methods for the determination of growth hormone are available.

It is our belief that the serum phosphorus level is a valuable aid in assessing the response of acromegalic patients to treatment; this is true when the initial level is abnormally high and also when it is about the upper limits of normal range.

The clinical response that we observed was encouraging and similar to the effects briefly mentioned by other investigators. The treatment of acromegaly is as yet far from satisfactory, and we believe that the use of estrogens offers an avenue of approach which should be explored further. Our patients were all women, and in our experience it does not seem feasible to administer these large doses of estrogen to men. Gynecomastia and loss of libido and potency, along with severe damage to

the testes, are serious complications of this treatment in men. Kinsell[15] suggests the combined use of estrogens and androgens in the treatment of acromegalic men. The effect of large doses of androgens in this disease to our knowledge has not been studied sufficiently.

We have not found the occurrence of uterine bleeding during estrogen administration a serious complication, and when it occurs we recommend a temporary increase in dosage.

Hurxthal, Hare, Horrax and Poppeu[25] have reported that six of seven patients receiving estrogens after surgical or x-ray therapy had further enlargement of the sella; one of these had impairment of the visual fields, and they think that these observations are a contraindication to the use of estrogens. To support this they cite Zondek's[26] observation of enlargement of the hypophysis of the rat during estradiol benzoate administration. Only one of our patients exhibited progressive visual disturbance, and that only after cessation of estrogen administration.

The results of this type of treatment have been encouraging in our brief experience, and we recommend its trial by others in patients in whom the method seems suitable.

Although x-ray treatment of the pituitary in acromegaly in the past has been unsatisfactory, improvements in technic may make it more useful in the future. Similarly, pituitary surgery for acromegaly to control only the metabolic aspects of the disease has, in our opinion, not yet reached a point where either the reduction in risk or improvement in technical management justifies our prescribing it. Improvements in technic and more complete replacement therapy may alter this part of the problem. Our report is offered to add to the accumulated knowledge of acromegaly and of diabetes rather than to recommend this method of treatment in preference to others.

SUMMARY

1. In six cases of acromegaly, treatment with large doses of estrogens resulted in pronounced clinical improvement.

2. All of the five patients with abnormal glucose tolerance curves showed reversal to normal or nearly normal values on estrogen administration. One showed a persistently decreased tolerance during therapy, which was improved, though not completely corrected, by increasing the dosage of estrogens (case 3).

3. All patients showed a sustained fall in serum phosphorus levels during estrogen administration. In one case the basal metabolic rate fell gradually to normal.

4. In the five cases in which hand volumes were observed a decrease occurred with estrogenic therapy, confirming the regression of acromegalic features.

5. Arterial hypertension appeared to be unaffected by this treatment.

6. The effects observed are believed to be due to inhibition of the production of growth hormone and possibly other closely related substances.

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SUMMARIO IN INTERLINGUA

Controlo de Diabete e Altere Aspectos de Acromegalia Post Tractamento a Estrogenos

1. In sex casos de acromegalia, un tractamento a grande doses de estrogeno resultava in pronunciate meliorationes clinic.

2. Cinque del patientes habeva anormal curvas de tolerantia a glucosa. In omne iste casos, le administration de estrogeno resultava in le retorno a valores normal o quasi normal. In un caso, le tolerantia a glucosa decresceva persistentemente durante le therapia. Isto esseva meliorate (ben que non corrigite completemente) per augmentar le dosage de estrogeno.

3. Omne le patientes monstrava durante le administration de estrogeno un persistente reduction del nivellos de phosphoro seral. In un caso, le metabolismo basal se abassava gradualmente a valores normal.

4. In le cinque casos in que volumines de mano esseva registrate, le therapia estrogenic resultava in un reduction de iste volumines. Assi le regression del tractos acromegalic pareva confirmate.

5. Le datos observate indicava nulle effecto del tractamento super hypertension arterial.

6. Le effectos producite per le tractamento esseva attribuibile, in nostre opinion, a un inhibite production de hormon de crescentia e possibilemente de altere substantias affin.

Nutritional Management of Children With Diabetes Mellitus

Shirley N. Wilkins, M.S., Doris Ott Ruby, M.S.,
Helen G. Kelly, M.S., and Robert L. Jackson, M.D., Iowa City

The maintenance diet of the child with diabetes mellitus should be essentially the same as for normal children.[1-8] We have had the unique opportunity of observing a large group of children with diabetes mellitus who have maintained a high degree of control of their disease throughout childhood. This was accomplished by using accurate doses of specific types of insulin in relation to the intake of a nutritionally complete diet adjusted to compensate for variations in physical activity. In this paper we shall present the caloric intake and growth curves for this group, compare the nutritional value of their diets with the 1953 recommended allowances of the National Research Council,[9] and discuss briefly the nutritional management of children with diabetes mellitus.

Forty-eight juvenile diabetics who maintained good control and attained normal growth, as measured by the Iowa growth charts,[10] were studied earlier to determine the insulin and caloric requirements in relation to age and growth.[11] The length of observation on a single subject ranged from three to eighteen years, the median for boys being seven years, nine months, and for girls seven years, eight months. To enlarge these serial data, observations from the records of five boys and six girls between the ages of one and six, and of twelve boys between twelve and eighteen years were included, making a total of 71 juvenile diabetics whose diets are evaluated.

In table 1 are listed the number of children studied and the number of observations at each age period. There are never more than two observations included for each subject in any yearly age group. The wide variation in number of data recorded at a single age and the number of years for which data are available are dependent on the age of onset of disease, the date of the first visit to this clinic, and the number of years during which the child maintained good diabetic control.

Both the parents and the children included in this study were given thorough instructions in dietary management. Periodic examinations were made at least every six months, at which time the diet was re-evaluated by the physician and the dietician. Any necessary changes were made so that the diet satisfied the appetite and was optimal for growth and development. The mothers of the diabetic children were instructed carefully at each clinic visit as to how to increase or decrease the caloric intake at any time necessary to meet the needs of the child. The foods were quantitated and records were kept. On days when more food was allowed for increased activity or less food was taken because of an infection or decreased activity, these changes were noted.

Tables 1 and 2 and figures 1 and 2 present the mean and standard deviations of the total caloric intake of the 39 boys and 32 girls. The total calories-per-day curves for the boys show a steady rise at least through age eighteen. The similar curves for the girls rise through age twelve, then level off and decline slightly. These caloric curves follow a pattern closely similar in slope to the standard height curves presented on the same charts. The average height and weight of the children, when plotted on the Iowa growth charts (figures 1 and 2), demonstrate that the boys and girls studied maintained normal growth. The individual growth charts based on serial observations showed no evidence of either undernutrition or overnutrition in any of the subjects.

In figure 3, the mean calories per pound of body weight for boys and girls are shown. It will be noted that the curves are almost identical through age ten. From one to three and one-half years the curves for calories per pound decrease rapidly; they level off until eight years of age, and then show a steady decline through adolescence. However, from age ten to eighteen, the calories per pound of body weight for girls decreased

From the Departments of Pediatrics and Nutrition, State University of Iowa, College of Medicine, Iowa City, Ia.

This study was aided in part by research grants from Burroughs Wellcome & Company, Inc., Eli Lilly & Company, and the National Institutes of Health, U. S. Public Health Service (No. A1-65 (C2).

Dr. Jackson's present address is: Department of Pediatrics, School of Medicine, University of Missouri, Columbia, Mo.

TABLE 1

Daily caloric requirements observed for boys

Mean and standard deviation of the total calories per day and the calories per pound of body weight per day for boys grouped according to age. The subjects are children with diabetes mellitus who maintained a high degree of control. The data also present mean heights and weights at the varying age groups to show that these children have grown normally.

Age (years)	No. of boys	No. of observations	Mean height (inches)	Mean weight (pounds)	Total calories per day		Calories per pound of body weight
					Mean	Standard deviation	Mean
2	2	3	36.0	30.3	1275		40.2
3	3	6	37.5	36.7	1350	88	35.4
4	8	14	41.0	42.1	1486	104	35.7
5	10	19	43.7	46.5	1631	86	34.0
6	10	18	46.7	53.4	1819	158	33.5
7	9	18	48.3	56.1	1858	239	32.9
8	11	22	50.8	62.0	2032	189	32.8
9	13	24	52.8	68.4	2113	192	30.9
10	13	26	55.3	77.9	2302	265	29.5
11	14	28	57.7	84.5	2383	231	27.7
12	16	32	59.6	93.0	2436	240	26.6
13	17	34	61.4	101.2	2599	254	25.6
14	18	36	63.9	112.8	2763	206	24.1
15	24	41	66.2	125.4	2930	285	23.7
16	21	42	67.7	135.2	3029	278	22.6
17	13	29	68.9	142.8	2977	328	21.0
18	11	22	70.1	154.4	2989	339	20.3

TABLE 2

Daily caloric requirements observed for girls

Mean and standard deviation of the total calories per day and the calories per pound of body weight per day for girls grouped according to age. The subjects are children with diabetes mellitus who maintained a high degree of control. The data also present mean heights and weights at the varying age groups to show that these children have grown normally.

Age (years)	No. of girls	No. of observations	Mean height (inches)	Mean weight (pounds)	Total calories per day		Calories per pound of body weight
					Mean	Standard deviation	Mean
1	5	5			1015	250	48.8
2	4	8	34.1	28.1	1131	138	40.3
3	4	8	37.5	33.7	1244	96	36.0
4	8	16	40.1	38.5	1347	135	35.3
5	9	18	42.6	44.0	1467	158	33.2
6	10	20	45.0	48.6	1593	186	33.0
7	10	20	47.6	54.7	1782	243	32.9
8	12	24	50.0	60.2	1921	174	32.5
9	13	26	51.2	66.2	1981	171	30.4
10	14	28	53.8	72.7	2052	226	29.1
11	18	34	56.6	82.5	2156	229	26.7
12	19	37	59.0	90.2	2246	328	24.4
13	20	39	60.8	101.6	2241	272	22.3
14	20	36	62.7	111.8	2177	265	20.2
15	18	30	63.3	117.5	2074	306	18.2
16	16	28	64.0	124.4	2097	297	17.5
17	14	26	64.8	130.4	2133	264	16.5
18	9	18	65.3	132.4	2020	168	15.3

more rapidly than those for boys. Figures 4 and 5 for these same data represent the ranges of calories per pound of body weight for boys and girls. At most ages the range is fairly wide, which illustrates that the caloric needs of each child are variable, depending not only on age and sex but also on body build, rate of growth,

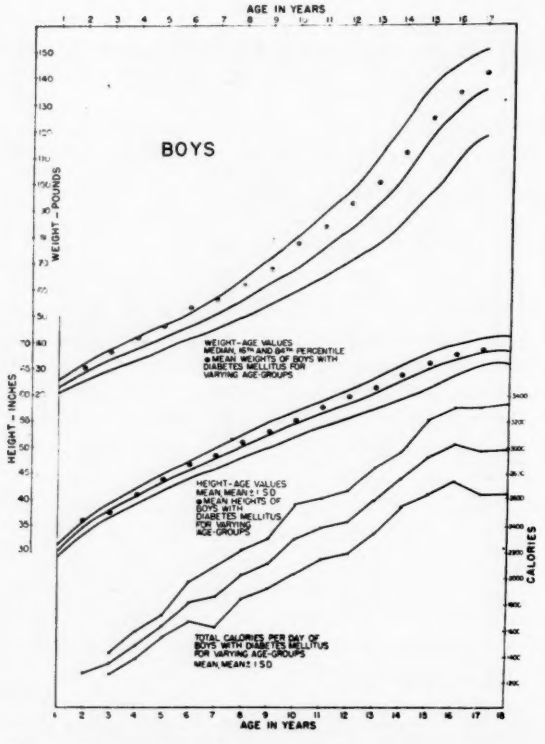

FIG. 1. Mean and standard deviation of total calories per day in relation to age for 39 boys with diabetes mellitus who maintained a high degree of control. Mean heights and weights of these same boys are plotted on the Iowa growth charts.

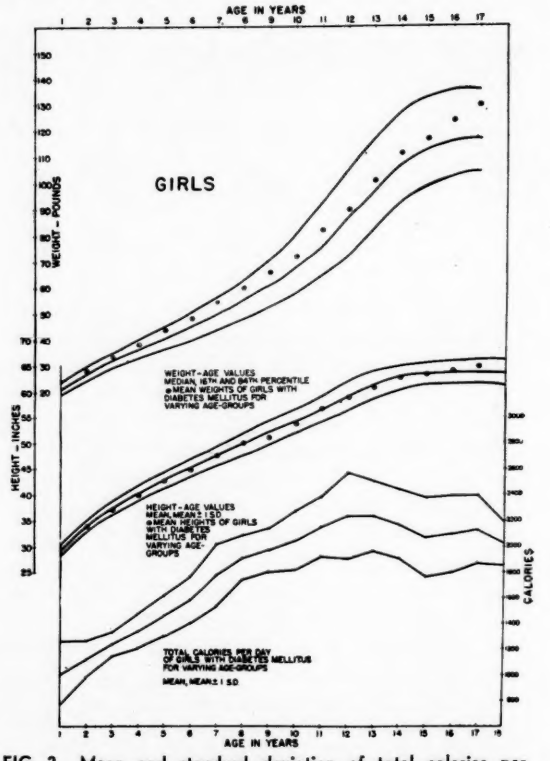

FIG. 2. Mean and standard deviation of total calories per day in relation to age for 32 girls with diabetes mellitus who maintained a high degree of control. Mean heights and weights of these same girls are plotted on the Iowa growth charts.

type and amount of activity, amount of rest, and emotional stress.

Tables 3 and 4 present the average daily nutrient intake of this group of diabetic boys and girls as compared with the daily dietary allowances recommended by the National Research Council (1953). It will be noted (starred values) that even though in several instances the caloric intake at a given age is lower than the NRC recommendations, the diets provide a more liberal allowance for protein, calcium, vitamin A, and riboflavin.

Figure 6 shows the curves of total and complete protein, that is, animal source protein, in the diets of the Iowa City boys as compared to the total and complete protein recommended by the NRC. Through age fifteen the complete protein available in the diabetic diets exceeds the total protein recommended. Likewise the total protein in our diets ranges from 16.5 to 18 per cent of the calories, as compared to 10.5 to 13 per cent in the NRC diets. The same relationship was found for the diets of the girls, and the curves are therefore not repeated here.

DISCUSSION

In 1932 at the White House Conference on Child Health and Protection[12] values for mean total calories per day were reported from studies including 253 boys and 243 girls. These data served as the basis for the caloric allowances recommended by the National Research Council. Since that time, dietary studies have shown that the calories furnished by the American diet very frequently are considerably below the NRC recommendations.[13] In the present study of 71 diabetic children who sustained essentially physiologic control and grew normally, the total caloric intakes of both boys and girls are much the same as the White House Conference data up to adolescence. However, from ages thirteen through eighteen for the girls and sixteen through eighteen for

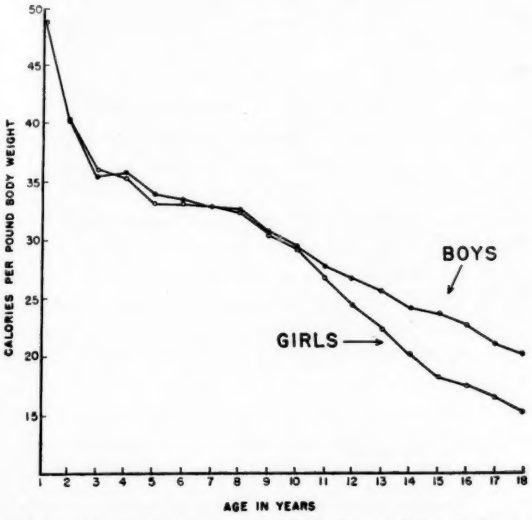

FIG. 3. Mean calories per pound of body weight in relation to age for 39 boys and 32 girls with diabetes mellitus in good control.

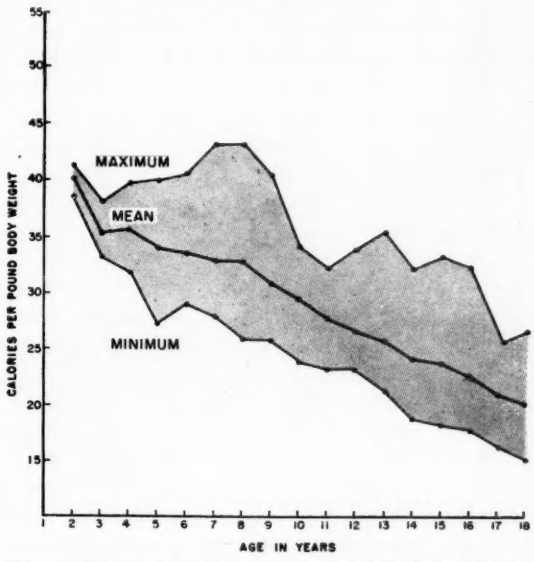

FIG. 4. Range of calories per pound of body weight in relation to age for 39 boys with diabetes mellitus in good control.

TABLE 3

Diabetic diets for boys

Diets used for boys in Iowa City Diabetic Clinic compared to daily dietary allowances recommended by the National Research Council (1953)

Age	Calories		Protein Gm.		Calcium Gm.		Iron Mg.		Vitamin A I.U.		Thiamine Mg.		Riboflavin Mg.		Ascorbic Acid Mg.		Vitamin D I.U.	
	Iowa	NRC	Iowa	NRC	Iowa	NRC	Iowa	NRC	Iowa	NRC	Iowa	NRC	Iowa	NRC	Iowa	NRC	Iowa	NRC
1-3	1200	1200	55*	40	1.1*	1.0	7	7	4700	2000	0.8	0.6	1.8*	1.0	110	35	400	
4-6	1500*	1600	65*	50	1.4*	1.0	8	8	5300	2500	1.0	0.8	2.2*	1.2	95	50	400	
7-9	2000	2000	90*	60	1.7*	1.0	11	10	6600	3500	1.4	1.0	2.8*	1.5	155	60	400	
10-12	2400	2500	105*	70	1.9*	1.2	13	12	8500	4500	1.6	1.3	3.1*	1.8	165	75	400	
13-15	2700*	3200	115*	85	2.4*	1.4	14	15	9000	5000	1.7	1.6	3.6*	2.1	165	90	400	
16-20	2900*	3800	120*	100	2.5*	1.4	16	15	9000	5000	2.0	1.9	3.8*	2.5	200	100	400	

TABLE 4

Diabetic diets for girls

Diets used for girls in Iowa City Diabetic Clinic compared to daily dietary allowances recommended by the National Research Council (1953)

Age	Calories		Protein Gm.		Calcium Gm.		Iron Mg.		Vitamin A I.U.		Thiamine Mg.		Riboflavin Mg.		Ascorbic Acid Mg.		Vitamin D I.U.	
	Iowa	NRC	Iowa	NRC	Iowa	NRC	Iowa	NRC	Iowa	NRC	Iowa	NRC	Iowa	NRC	Iowa	NRC	Iowa	NRC
1-3	1100*	1200	55*	40	1.1*	1.0	7	7	4400	2000	0.8	0.6	1.8*	1.0	110	35	400	
4-6	1400*	1600	60*	50	1.4*	1.0	7	8	5300	2500	0.9	0.8	2.1*	1.2	95	50	400	
7-9	1900	2000	80*	60	1.5*	1.0	10	10	6000	3500	1.2	1.0	2.4*	1.5	140	60	400	
10-12	2200	2300	100*	70	1.9*	1.2	12	12	6900	4500	1.4	1.2	3.0*	1.8	140	75	400	
13-15	2200*	2500	100*	80	1.9*	1.3	12	15	6900	5000	1.4	1.3	3.0*	2.0	140	80	400	
16-20	2000*	2400	90*	75	1.7*	1.3	11	15	6500	5000	1.4	1.2	2.8*	1.9	140	80	400	

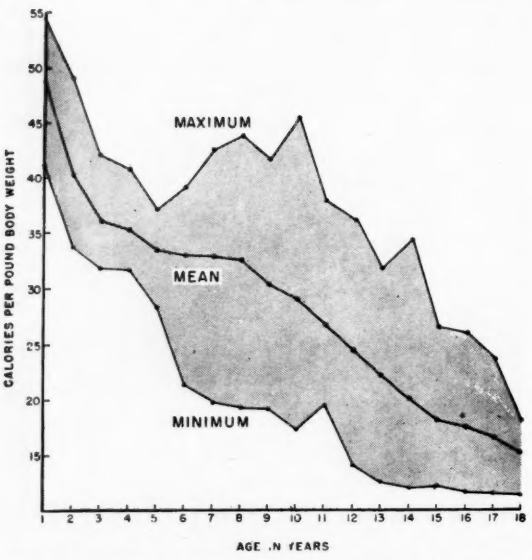

FIG. 5. Range of calories per pound of body weight in relation to age for 32 girls with diabetes mellitus in good control.

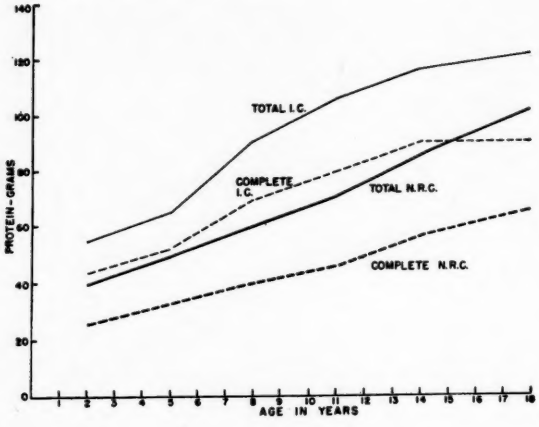

FIG. 6. Curves of total and complete protein in the prescribed diets of Iowa City (I.C.) boys at varying ages as compared to the total and complete protein in diets recommended by the National Research Council (NRC). The complete protein for the I.C. diets is the animal protein calculated from typical diets appropriate for given ages. The NRC complete protein has been calculated as 2/3 of the total protein values for each age.

the boys, these children receiving semi-quantitated diets have somewhat lower caloric intakes. As mentioned previously, so many factors determine the total caloric requirement that very large deviations from the mean intake must be expected. The wide range in caloric intake (figures 4 and 5) at a particular age for both boys and girls demonstrates that intake must be governed by variations in activity and stage of maturation in order to sustain normal growth. Therefore it is not possible to predict exactly the caloric requirement of any given child, but the general pattern or curve that this intake will follow can be anticipated.

This knowledge is particularly useful in guiding the intake of adolescent girls to prevent the overweight frequently noted during this period. For girls after the age of twelve years, the mean total calories-per-day curves reflect a decreased intake, and the calories-per-pound curve for girls during postpubescence shows a rapid and steady decline. Some of the factors involved in the usual accelerated weight gain are failure to decrease insulin and caloric intake after the prepuberal growth spurt, decreased physical activity, and dietary indiscretions to attain social acceptance. Since these girls were receiving weighed diets and their growth and weight gain were being evaluated every three to six months, it was possible to advise decreasing the caloric intake before the overweight became excessive.

A tendency to overweight did not appear in the boys, the total calories-per-day curves showing a steady upward trend through adolescence. Boys continue to add weight during late adolescence after height growth has been essentially completed; also, the amount of physical activity of boys frequently increases.

We realize that figures 1 and 2, which give mean total caloric intake for boys and girls, should be used only as a general guide, since a wide range is to be expected due to the adjustment of the diet, primarily for varying physical activity. A discussion of physical activity in juvenile diabetics has been presented by Jackson and Kelly,[14] who point out that during short periods of increased exercise it is better to give additional food than to decrease the amount of insulin to compensate for the increased physical activity. Normal children may be expected to have increased appetites and to take extra food for exercise so that their needs for growth will continue to be met. The same is true for the well regulated diabetic child, and with instruction and experience these children and their parents have learned how to adjust their diets and still maintain essentially physiologic control of their disease.

Recent research by a group of workers at Columbia University[15, 16] has given us some data on energy expenditure by children for specific activities. These data aid in demonstrating that caloric intake might well in-

crease several hundred calories a day to meet the needs of periods of strenuous activity. For example, Taylor[15] states that boys of twelve to fourteen years of age would require 2.1 cal. per kg. per hr. for quiet play, with an increase to 4.5 cal. per kg. per hr. for cycling. The mean value for energy expenditure for the routine activities of the twelve- to fourteen-year-old diabetic on this study is 2.6 cal. per kg. per hr. An increase of 1.9 cal. per kg. per hr. would bring the calories up to Taylor's requirement for cycling. For a thirteen-year-old boy of average weight, 42 kg., this would add an energy expenditure of 80 cal. per hr. Four hours of work at this rate of expenditure would add approximately 320 calories to the day's needs. Therefore the predicted mean total caloric intake for a thirteen-year-old boy might increase from 2600 to 3000 calories or more on a day when physical activity is increased. It is obvious that exercise is an extremely important factor in determining total caloric needs; therefore the curves presented here should be used only as a general guide and should be individualized for each patient.

It should also be pointed out that the mean calories per pound of body weight have been calculated from caloric intakes and weights of well regulated diabetic children. These calculations represent their everyday maintenance and growth requirements. The caloric needs of a newly discovered diabetic who has become undernourished with the onset of the disease or is not fully utilizing his food would be expected to be higher than the maintenance requirements for a well regulated child, since there is a need to rebuild body tissues and replenish body stores. Once good nutritional status has been re-established and growth is following a fairly normal pattern, caloric requirements can be estimated by these mean calories-per-pound figures. However, if a child is either overweight or underweight the theoretical weight for his height rather than his actual weight should be used as a guide in predicting caloric intake.

As stated earlier, the diets for children with diabetes mellitus should approximate the diets for normal children. However, considerable emphasis has been placed on the use of a higher protein diet for diabetics. The main effect of diabetes on protein metabolism appears to be a decreased rate of muscle protein synthesis. In untreated severely diabetic animals, this decrease in formation rate may be as high as 60 to 80 per cent.[17] In the studies of the effects of protein on blood sugar levels of diabetic patients, Till[18] confirmed the importance of protein in maintaining an even distribution of sugar in the blood. Schwarz[19] has stated that a high-protein diet may be valuable in the prevention and treatment of diabetic retinopathy. Fanconi and others[20] report an extremely high incidence of nephropathies in a group of juvenile diabetics given a low-protein diet.

Almost all juvenile diabetic patients are labile and at times do not maintain a high degree of control of their disease. A higher protein intake is therefore advised to re-establish the nutritional state after periods of incomplete control, to provide greater satiety value in the diet, to help maintain more even distribution of sugar in the blood, and possibly to retard the development of degenerative changes.

The requirements for water-soluble vitamins such as thiamin may also be higher for the diabetic patient during periods of incomplete control. Ott[21] reports that larger amounts of thiamin are excreted by diabetic rats than by normal rats. Myers,[22] working with diabetic children and young adults, found that the diphosphothiamin fraction of the blood was somewhat lower among diabetics, particularly among poorly controlled patients.

Nutritional management of the diabetic child implies not only the what or why of the diet but also the how. To provide a liberal diet, rich in protective foods and adjusted to meet the needs of each individual child, is the first objective of dietary management. As reported by Jackson and Kenefick,[4] the diet is calculated on the basis of protein and calories, and no special attention is given to the fatty acid:dextrose ratio of individual meals. The diets are liberal, permitting a wide variety of foods, but excluding concentrated sweets. Frequently the nutrition of the entire family is improved by using the diabetic's meal pattern.

Many hours of teaching and demonstration were spent with each family so that the fundamentals of good nutrition could be learned and applied to every member of the family. In the beginning, in order to learn the caloric content of different portions of a food, the mother and diabetic child were taught how to weigh all the foods for the diet. Soon the mother learned to estimate the foods that appeared daily in the meals. Then, recipes combining the basic foods used in the diet were given to the patients, which added variety to the meals and stimulated individual interest. Finally, the patients were instructed in the use of the diabetic diet exchange lists[23] to prepare them to fit into the diet pattern widely used by adult diabetics. They were frequently reminded, throughout their training, of the need to increase or decrease the diet to compensate for differences in physical activity. In addition they were taught how to adjust the basic diet according to the appetite and rate of growth.

In recent years, with the use of longer-acting types of insulin, the diet pattern of the diabetic has simulated the usual dietary habits of well-fed nondiabetic children. The diabetic is given prescribed lunches to take between meals; this provides greater opportunity to increase or decrease food intake for daily variations in physical activity and also helps the social adjustment of the child.

Controversy still exists as to whether the diet should be given quantitatively and at specific periods during the day, or whether the child should simply be allowed to eat a supervised diet. The introduction of the term "free diet" has resulted in considerable confusion, since the term is interpreted differently by different people. In our opinion it is not desirable to permit any child, diabetic or otherwise, to eat without some supervision and direction. A large percentage of American children are receiving inadequate diets because of excessive intakes of unessential foods. This type of eating pattern should be discouraged for all children. The only difference in the dietary program for the diabetic as compared to the nondiabetic child, according to our regimen, is that we plan the diet so that he has a predictable intake given in the proper relationship to the type and amount of insulin that has been administered to avoid glycosuria and insulin reactions.

None of the patients included in this study had any clinical evidence of vascular disease. As part of a current study of degenerative changes in juvenile diabetics, we have been carefully reviewing at this clinic the dietary habits of patients who have had their disease for more than ten years. The data clearly show that those patients who have established good nutritional habits during childhood have, with few exceptions, carried these habits into adult life. Furthermore, there is an extremely low incidence of hypertension and albuminuria even in some of the patients who have not maintained a high degree of control as judged by glycosuria. It may well be that the lowered incidence and severity of degenerative changes in our patients may be related to their good dietary habits.

SUMMARY

A serial study of caloric intakes of 71 juvenile diabetics who sustained normal growth is presented. This information taken during childhood and adolescence has added to our understanding of the total energy requirements of boys and girls, the caloric requirements per pound of body weight, the differences in requirements for sex and activity, and the need for a reduction in calories for girls shortly after maturation. Curves based on the mean and standard deviaton of total calories per day for varying age groups and the mean calories per pound of theoretical body weight have been derived from these data and may be used as a general guide for caloric requirements for children and adolescents.

A comparison of the nutritive value of the diabetic diets with the allowances recommended in 1953 by the National Research Council illustrates that, even though caloric intakes in general are lower than those recommended, the diets provide a more liberal allowance of protein, calcium, vitamin A, and riboflavin.

The maintenance diet for the diabetic child should be essentially the same as for the well-fed normal child; and in our opinion the diet should be planned quantitatively, with foods given at specific periods during the day. The diet should be individualized to meet the varying needs of growth, physical activity, and maturation pattern of each child. Inasmuch as it is impossible to maintain complete diabetic control at all times, a slightly higher intake of protective foods is advised to provide some margin of safety.

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SUMMARIO IN INTERLINGUA

Regime Nutritional pro Infantes con Diabete Mellite

Es presentate un studio serial del rationes caloric de 71 diabeticos juvenil qui manteneva un crescentia normal. Le information hic colligite ab juveniles e adolescentes augmenta nostre comprension del requirimentos de energia total in pueros e pueras, del requirimentos caloric per libra de peso corporee, del differentias inter le requirimentos pro le duo sexos e pro varie grados de activitate, e del necessitate de reducer le ration caloric de pueras brevemente post lor maturation. Nos ha utilisate nostre datos in le elaboration de curvas del deviation median e standard del rationes caloric total per die pro varie etates e del ration caloric median per libra de peso corporee theoric. Iste curvas es usabile como guidas general pro determinar le requirimentos caloric de juveniles e adolescentes.

Nos ha comparate le valor nutritive del dietas diabetic in nostre serie de casos con le recommendationes publicate in 1953 per le Consilio National de Recerca. Iste comparation indica que le rationes caloric in nostre serie esseva generalmente inferior al recommendation del Consilio sed que le provision de proteina, calcium, vitamina A, e riboflavina esseva superior.

Le dieta currente pro juveniles diabetic deberea esser essentialmente identic con illo de ben-alimentate juveniles normal. In nostre opinion, le dieta del juveniles diabetic deberea esser planate quantitativemente con alimentos prendite a periodos specific del die. Le dieta deberea esser individualisate pro satisfacer le varie requirimentos de differente combinationes de crescentia, typos de activitate, e maturation. A causa del impossibilitate de un complete e nunquam interrumpite controlo diabetic nos recommenda un leve augmento de alimentos protective pro provider un certe margine de securitate.

Neurologic Complications Associated with Diabetes

Allan A. Bailey, M.D., Rochester, Minnesota

Evaluation of neurologic complications in diabetes mellitus calls always for extremely critical appraisal. Things are not always what they seem to be, and the mere fact that certain neurologic deficits have been credited for many years to diabetes may mislead physicians in the investigation of a given problem or blind them to new avenues of research. The literature contains an abundance of clinical studies on large and small groups of patients, although it is surprising how little solid work has been done in neuropathology. Attention has been focused especially on the more troublesome and painful symptoms traceable to involvement of the peripheral nerves. The term "diabetic neuritis," or the more commonly used "diabetic neuropathy," is familiar to all physicians. In fact the mere occurrence of diabetes and neuritis in the same patient may lead to the inference that the patient has diabetic neuritis, when closer scrutiny of a particular neuritic manifestation would have reminded the physician that the problem should have been looked at from a broader point of view. This presentation first takes up the subject of peripheral neuritis and then proceeds to consideration of involvement of the spinal cord, brain and cranial nerves in patients who have diabetes mellitus.

DIABETIC NEUROPATHY

The subject of diabetic neuropathy recently has been splendidly reviewed by Goodman and others.[1] The incidence of neuropathy varies greatly. For example, Joslin and associates,[2] in 1928, gave an incidence of 0.1 per cent in their series, while Collens and co-workers[3] reported an incidence of 93 per cent. However, if all degrees of neuropathy are included, it appears that the clinical incidence is approximately 50 per cent, whereas the incidence of clinically significant diabetic neuropathy is probably less than 5 per cent. Neuropathy tends to occur in older patients and in those who have had diabetes more than 5 years. However, a significant number of exceptions to these generalizations are present; sometimes the symptoms appear in infants and children and occasionally the onset of neuropathy appears to be coincident with the onset of the diabetes itself or even with treatment. It appears to antedate the appearance of diabetes in a few patients. As a neurologist I have been led to speculate about the possible cause of neuropathy in a patient who has no evidence of diabetes but who has a strong family history of diabetes and no other cause ascertainable for his disorder. It is also of interest that diabetic retinopathy is sometimes present before other clinical and laboratory evidence of diabetes appears.

General Clinical Features. It might be more appropriate to speak of the diabetic neuritides, since the peripheral nerves in diabetics may be affected in different ways and probably by different causes. The patient may have much pain but present none of the usual subjective signs of neuritis other than increased tenderness in the calves; conversely, he may have no pain but present a wealth of signs. Sensory loss may be unaccompanied by paralysis; contrariwise, paralysis may be grave and sensory impairment almost insignificant. The larger vessels of the feet may be open or closed. The content of protein in the cerebrospinal fluid at the time of examination may be increased or may be normal. The course may be relatively acute and severely disabling but end in complete restitution, or the disease may be insidious and steadily progressive. The vagaries are so numerous as almost to defy classification.

It is often impossible for the clinician to differentiate between peripheral neuritis and radiculitis, involving single or multiple nerves. This is not only true of neuropathy in diabetes but is an almost constant difficulty for the neurologist in the field of these disorders regardless of cause. The electromyogram is allowing greater insight into this problem. The commonest symptom of diabetic neuritis probably is pain in the legs, particularly in the calves, with or without exquisite hyperesthesia over the body or lower extremities. The pain is often worse at night. Numbness of the feet

From the Section of Neurology, Mayo Clinic and Mayo Foundation, Rochester, Minn.

The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

Read at the Postgraduate Course of the American Diabetes Association, Rochester, Minn., January 18-20, 1954.

and toes is a common complaint. Muscular weakness as a symptom is relatively rare.

The early signs of the neuropathy consist of tenderness in the calf muscles, absent Achilles reflexes and, later, absence of patellar reflexes. Loss of vibratory sensibility at the malleoli and in particular at the toes is one of the earliest objective signs, although occasionally loss of sensations of pain and temperature is more outstanding in the sensory examination. Special comment about vibratory sensation is in order. It is generally agreed that vibratory sensibility decreases with age but the degree of this loss and the variabilities within any one decade of life generally have not yet been agreed on. For example, complete loss of vibratory sensibility in the toes and a reduction at the malleoli might well be present in a patient more than 60 years of age and have no special meaning as evidence of neuropathy. However, the same findings in a patient in earlier decades of life would be significant. Thus, it is unwise to base the diagnosis of neuropathy on the presence of a single objective finding without due consideration of other explanations for it. In years past, loss of vibratory sense and impairment of sense of position in the toes have been spoken of as "posterior column" signs. This is a misnomer as these signs may appear in patients who have peripheral neuritis, intraspinal radiculitis or disease of the spinal cord; loss of sense of position may occur, of course, from lesions in the thalamus or cortex.

Classification. Several attempts have been made to classify the neurologic complications of diabetes and in particular to classify the various types of neuropathy.[4,5] None of these is too satisfactory and much overlapping occurs from one type to another. Difficulties are enhanced because knowledge of the pathologic anatomy is surprisingly defective.

In general, neurologic complications of diabetes may be divided into those that are related in some way to disturbed metabolism and those that are secondary to the associated vascular changes so common in diabetes. In the brain, it is the vascular process that is of clinical importance. As for peripheral neuropathy, metabolic and vascular factors are probably of equal importance, although the importance varies in different patients. In a group of patients studied by Woltman and Wilder,[6] in 1929, ischemia and infarcts were clearly seen, with consequent degenerative phenomena in the nerves. These findings are perhaps evidence of the terminal phase of the process. Before the common clinical groupings of the neuropathies are mentioned, some reference to dysfunction of the autonomic nervous system is in order. Such dysfunction is manifested by loss of ability to sweat, trophic disturbances of the feet and toes, orthostatic hypotension and gastrointestinal symptoms, including diarrhea and constipation. Sexual impotence is not uncommon in severe neuropathies. Urinary incontinence or retention due to neuritis of the pudendal nerves or sacral radiculitis is not an uncommon accompaniment of diabetic neuropathy and I have seen it appear rather early, along with such an unusual symptom as a sensory ataxia. Sometimes it is accompanied by much pain over the buttocks and posterior aspect of the thighs.

All these disorders are important occasional manifestations of diabetic neuropathy. Again, emphasis must be placed on the need for careful studies by the neuropathologist. How much of this trouble is due to faulty function in the sympathetic nervous system and how much is due to disturbances in peripheral nerves, or in the anterior roots within the spinal canal, is unknown. Perhaps the physiologists soon can give more help with these questions.

In the classic picture, either symmetrical multiple neuritis or multiple radiculitis or combinations of both are present. One group of patients has diabetes with pain. These pains may be rather diffuse, involving the arms and back as well as the lower extremities, but objective findings are relatively absent, apart perhaps from tenderness in the calves. The pain is characteristically worse at night; in these situations, the diabetes is usually out of control and the symptoms improve when it is brought under control. This situation appears to be a reversible process due to some metabolic disturbance associated with poor control of the diabetes. It is agreed that these symptoms are alleviated when the diabetes is brought under control. Most of these patients experience symptomatic relief but some observers[7] state that a few patients when seen years later apparently have suffered from progressive neuropathy.

The patients in the second group have minimal symptoms, if any, and a few objective signs such as loss of an ankle jerk and reduced vibratory sensibility. The course of the neuropathy appears to be relatively benign and asymptomatic as long as the diabetes is under satisfactory control. The condition in some of these patients undoubtedly progresses so that they are included in the third group of patients, in whom we see pronounced symptoms and signs and in whom great disability occurs, due to pain, muscular weakness or serious sensory and trophic disturbances, which are

often unassociated with obvious arteriosclerosis of the larger peripheral vessels. The incidence of an increase in the total protein in the cerebrospinal fluid is at least 50 per cent in this group. In addition to the serious cutaneous disturbances in the feet, Charcot joints are occasionally seen in diabetic neuropathy. The sensory loss, especially for temperature, is great in these patients.

The fourth group of patients includes those who have a picture rather similar to that of neuronitis. These patients have diffuse severe pains in various parts of the body, weakness of the muscles, tender calves and sometimes atrophy. The predominant signs are in the lower extremities, where muscular weakness is usually pronounced. The protein in the cerebrospinal fluid is increased, sometimes to as much as 400 mg. per 100 cc., although usually it is between 80 and 150 mg. Partial or complete recovery apparently occurs in these patients over a long period. It is likely that the disturbances are in the central nerve roots and in the peripheral nerves, although some investigators have attributed these disturbances to disorders in the spinal cord. However, studies of pathologic anatomy of the spinal cord in diabetics are few and limited in scope, and the clinical studies reported are not convincing. As already mentioned, the classic neurologic disturbances of diabetes are those of peripheral neuritis or radiculitis or both. These disturbances most likely are due to some metabolic factor. Doubtless in some instances the neuropathy is due to ischemia as a result of an arteriosclerotic process in the vaso-nervorum of the peripheral nerves. However, all this may be an end result of a long process rather than the cause of an initial disturbance which gave rise to symptoms of neuropathy many years before the death of the patient or the amputation of a limb. The work of Woltman and Wilder is still classic in regard to this problem.

At one time it was considered that diabetes was a common cause of femoral neuritis, sciatic neuritis, peroneal palsy and ulnar palsy. In fact, if diabetic neuropathy was explained as always being due to infarcts in the nerves, then examples of such palsies should be more frequent than they are in diabetic neuropathy. On the other hand, it is a fact that the predominant symptomatic picture is that of multiple neuritis in the lower extremities. Therefore, the presence of mononeuritis should be regarded with suspicion and physicians should look for such factors as cross-leg paralysis and armchair or desk palsies of the ulnar nerves. Due regard should be given to the probability that sciatic neuritis, femoral neuritis and brachial neuritis may be examples of localized extraspinal lesions or intraspinal disorders, such as protruded intervertebral disks, hypertrophic ridges or even intraspinal tumors. Such unassociated conditions can occur in the presence of diabetes. Physicians must avoid the pitfall once so common in the evaluation of patients who had syphilis, namely that one disease capable of causing neurologic disorders is likely to be the cause of all neurologic deficits in the patient's lifetime.

Friedreich's ataxia combined with diabetes mellitus has been reported in more than one member of the same family. In one report, optic atrophy was also present; I have seen this situation on one occasion. The genetic aspects of this problem need further study. It should be noted that the ataxia precedes the diabetes; therefore, it is unlikely that the metabolic disturbances of diabetes are the cause of this syndrome.

Palsies of Cranial Nerves. Palsies of cranial nerves, particularly ocular palsies, due to diabetes, need more evaluation. Here again data are needed from the pathologic anatomist as to the site and type of the lesion seen in these patients. It has been accepted for a long time that diabetes could cause ocular palsy; the sixth nerve in particular has been prone to succumb to the effects of the disease. Rucker[8] and his colleagues in the Section of Ophthalmology at the Mayo Clinic have been making a survey of ocular palsies. Of 276 patients who had palsies of the third, fourth and sixth cranial nerves, only 10 patients were diabetic. The majority of these palsies in diabetic patients were associated with moderately severe hypertension; several patients had severe diabetic retinopathy. The third nerve was implicated in 2 patients, the fourth nerve in 2, the third and fourth nerves in 1 and the sixth nerve in 5. The pupils were not abnormal in any instance. The patients were all in the older age groups and the type of palsy suggested that the lesion was intramedullary rather than in the nerve itself. In view of the facts that such palsies are not uncommon in patients who do not have diabetes and that metabolic and toxic factors usually do not cause such lesions, I am not inclined to look on diabetes as the primary cause of palsies of cranial nerves. The review of Waite and Beetham[9] on visual disorders in diabetic patients is a classic. They stated that the onset of ocular palsy did not appear to bear any relationship to the value for blood sugar or the duration of diabetes. It was their impression that these palsies were due to a vascular lesion and they suspected hemorrhage. A tiny infarct in the pontine or midbrain

area appears to be the most likely explanation to me.

The pupils of patients who have even uncomplicated diabetes are often extremely difficult to dilate with any combination of drugs. Abnormalities of the pupillary reflexes are seen occasionally. These may be minor but a few patients have typical Argyll Robertson pupils. As in syphilis, the site of the lesion causing such abnormalities is unknown. The Argyll Robertson pupil has been noted in patients who have such pronounced evidence of radiculoneuropathy that the term "tabes diabetica," or "diabetic pseudotabes," has been used to designate the combined findings.

Facial palsy has been reported to be associated with diabetes but the relationship is questionable. Palsies of the vocal cords are rarely observed and the cause is often unknown in diabetic and nondiabetic alike. Dysfunction of the eighth nerve has been reported. A recent experience in a 40-year-old woman who had severe complicated diabetes is interesting. This patient had experienced sudden unilateral loss of hearing with recovery a year ago and then a few months ago had become completely deaf in the same ear. One might be tempted to assign the term "eighth-nerve neuritis." However, repeated tests of labyrinthine function were normal; she probably had a tiny vascular lesion in the cochlea.

Bilateral palsies of cranial nerves have been recorded in patients who had a picture of diffuse polyradiculitis. These patients eventually made a good recovery.

Thus it appears unlikely that isolated palsies of cranial nerves are due to metabolic factors; at least, such palsies should not be attributed to diabetes mellitus without careful consideration of other possible causes for the palsy. If they are related to diabetes, it is likely they are due to tiny vascular lesions; the prognosis is usually good.

Treatment. The present-day treatment of diabetic neuropathy leaves a great deal to be desired. It is generally agreed that satisfactory control of the diabetes must be obtained; this is not always easy. The use of vitamin B complex or vitamin B12 in large doses has been rather consistently disappointing in either relieving pain or stopping progression of the neuropathy. The use of liver extract from pregnant mammals or dimercaptopropanol (BAL) has not been of value. The treatment of pain is often a major problem, and sometimes codeine or even meperidine hydrochloride (demerol) must be given for a short period. However, because of the chronicity of the disease, addiction or at least serious dependency on the drug is a constant risk.

In the treatment of muscular weakness, splints may be necessary for footdrop and wristdrop; the patient should be warned to avoid pressure on the ulnar or peroneal nerve as he sits around or lies in bed. It is important to insure adequate emptying of the bladder when sphincteric dysfunction is present. Sometimes slight obstruction of the vesical neck will need the attention of the urologic surgeon. The feet should receive constant and special attention.

CEREBROVASCULAR LESIONS

The association of vascular lesions with diabetes is well recognized. The brain is frequently involved; Root and Kenny[2] reported 231 instances of focal cerebrovascular lesions in a series of 913 patients who had neurologic disorders associated with diabetes. There was nothing peculiar about the site of the lesion or the prognosis in this group of patients. Twenty of these 913 patients had paralysis agitans; this incidence is probably not remarkable in view of the age of the majority of the patients.

EPILEPSY

The incidence of epilepsy is no greater in more complicated adult diabetic patients than it is in the general population. However, it is possible that a hypoglycemic reaction may trigger seizures in susceptible patients.

At one time it was suggested that patients who had electro-encephalographic evidence of cerebral dysrhythmia and who had a high incidence of hypoglycemic reactions when under treatment for diabetes should be treated with anticonvulsants. In my experience anticonvulsants have not been useful in these situations and my associates and I recommend use of anticonvulsants only for patients who actually are having evidence of clinical epilepsy in some form or other; the epileptic disorder is treated in the same way it would be if the patient did not have diabetes.

SUMMARY

The outstanding clinical manifestation in the neurologic complications of diabetes is peripheral neuropathy. This is usually associated with some involvement of the nerve roots. No good evidence exists that the spinal cord is ever significantly affected. Patients who have palsies of the cranial nerves and patients who have symptoms of mononeuritis or monoradiculitis require particularly careful neurologic evaluation with a view to other possible causes of these monosymptomatic syndromes.

Not all of the neurologic problems in diabetic patients are necessarily of diabetic origin. On the other hand, diabetes always should be seriously considered when a patient has evidence of neuritis.

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SUMMARIO IN INTERLINGUA

Complicationes Neurologic Associate con Diabete

Inter le complicationes neurologic de diabete, le manifestation clinic per excellentia es neuropathia peripheric. Isto es generalmente associate con alicun affection del radices nerval. Il non existe un convincente demonstration que le corda spinal es unquam afficite de maniera significative. Patientes con paralyse del nervos cranial o con symptomas de mononeuritis o monoradiculitis require un cautissime evalutation neurologic pro determinar le possibile presentia de altere causas de lor syndromes monosymptomatic.

Non omne le problemas neurologic in diabeticos es necessarimente de origine diabetic. Sed del altere latere, le presentia de diabete debe semper prender se in consideration quando un patiente exhibi signos de neuritis.

The Psychiatric Aspects of Obesity

Psychiatric experience with obese patients shows a wide variety of conflicts and psychiatric syndromes. While many patients have some features in common, it is unsafe to generalize about common factors in the single case. Every patient is an individual whose life patterns are distinctive for him. It is best for the physician to permit the patient to reveal as much of his own patterns as possible and not depend on descriptive formulas that may be only partially applicable to the patient under consideration. When the patient first comes for help, both physician and patient act as if the patient has a strong wish to reduce. Later it becomes obvious that some obese patients simply cannot deny themselves food no matter what social pressures are being exerted on them. The physician from the outset attempts to support the patient's wish to reduce and make the mechanics of eating fewer calories as comfortable as possible. The use of special regimens for checking weights, diets, laboratory tests, serial photographs, and charts for dramatic portrayal of weight changes are all useful methods for giving the patient the added attention required during the periods of distress. If the patient falters from time to time, both the patient and the physician act as if they can overcome the forces that caused the lapse. This commonsense method is often successful in patients with strong internal motivation to reduce. The doctor need not be either surprised or angry if he finds that in more severe cases the patients cannot refrain from excessive intake, nor will they tell the truth when questioned. It will be remembered that the susceptible patient faces many temptations to eat if he goes out socially to cocktail and dinner parties or picnics, and that he is often ridiculed if he attempts to abstain. The external pressures from friends and the family severely compound the inner struggle between the wish to be thin and the hidden internal rewards that come with overeating and large size. The deep-seated nature of this struggle may not appear until the patient has been following a diet for several weeks and finds himself more anxious and tense from the increased threats that come with the weight loss. Many patients will diet in a rigid manner until they cannot tolerate the loss. Some patients relapse into their old eating habits or have a period of severe emotional distress after completing a reducing regimen, thus calling our attention to the persistence of the inner motivation to be overweight.

From "The Psychiatric Aspects of Obesity,"
by Henry W. Brosin, M.D.,
in *J.A.M.A.*, July 31, 1954.

Protein-Bound Carbohydrate in the Serum of Diabetic Patients With and Without Vascular Complications

Nils Rud. Keiding, M.D., and Elizabeth F. Tuller, Ph.D., Boston*

Since the demonstration of carbohydrate-staining material in the lesions of diabetic nephropathy and diabetic retinopathy by McManus[1] and Friedenwald,[2] respectively, there has been increasing speculation as to the possible relationship of the protein-bound carbohydrate of the serum and the formation of the histologic lesion.[1, 3, 4] The importance of these lesions as well as reports pointing to a correlation between the carbohydrate-staining property of tissue and the concentration of certain carbohydrate-protein complexes of serum[5, 6] prompted a study of these substances in the serum from diabetics, and such work was initiated in our laboratory in 1951.

There has been some indication that higher levels of protein-bound carbohydrate may be found in diabetics,[7, 8] although other scattered reports have presented only normal levels.[9, 10] No attempt has been made in these publications to correlate any of the above-mentioned findings to the presence of vascular degenerative disease in the diabetics.

More recently, systematic studies of the protein-bound carbohydrate in the sera of diabetics, particularly with respect to a possible relationship of any changes to the presence of the diabetic vascular lesions, have been made by Berkman and his associates,[11] Nielsen and Poulsen,[12] and by us. Berkman, Rifkin and Ross report that the concentrations of the protein-bound non-hexosamine carbohydrate in a total serum protein precipitate and in a serum mucoprotein precipitate are not increased in diabetic patients without clinically detectable degenerative vascular disease. However, these substances as well as total serum glucosamine are increased in the diabetics with vascular complications. Nielsen and Poulsen report similar results in the work done on the total non-hexosamine and total hexosamine constituents. In addition, they analyzed fractions separated by salting out with 50 per cent ammonium sulfate and found that the elevation of carbohydrate content with the vascular complications took place principally in the albumin fraction.

This paper reports the results obtained in our study of the protein-bound carbohydrate found in the serum mucoproteins and in the total serum proteins of diabetics with and without the degenerative vascular lesions, retinopathy, and nephropathy.

MATERIAL

The 81 diabetic subjects were patients in the New England Deaconess Hospital. Those exhibiting complications such as infections, tumors, or nondiabetic kidney disease were excluded. None were in a state of ketosis or coma. Blood samples were taken in the fasting state or three hours after the morning meal.

The patients were divided into groups according to the presence or absence of two major vascular degenerative lesions of diabetes: retinopathy and nephropathy (characteristics of these complications have been described in an earlier report[13]).

Group D-1: Diabetics with no signs of retinopathy or nephropathy. In 32 patients the age ranged from 17 to 68 years (average 43 years) and the duration of diabetes from 0 to 28 years (average 8 years).

Group D-2: Diabetics with minimal to moderate retinopathy but without nephropathy. The age in 18 subjects ranged from 20 to 60 years (average 39 years) and the duration from 7 to 31 years (average 12 years).

Group D-3: Diabetics with advanced retinopathy but no clinical signs of nephropathy. In 15

From the Baker Clinic Research Laboratory, New England Deaconess Hospital, Boston, Mass.

This investigation was supported in part by grants from the Diabetic Fund of Boston and by the Nordisk Insulin Fond.

*Steno Memorial Hospital, Gentofte, Denmark.

Address communications to Dr. Tuller, Baker Clinic Research Laboratory, Boston, Mass.

subjects the age range was 23 to 72 years (average 50 years). The duration was from 7 to 31 years (average 20 years).

Group D-4: Diabetics with marked retinopathy and evidence of diabetic nephropathy. Of 16 patients, 8 had blood nonprotein nitrogen values exceeding 40 mg. per 100 ml. The age range was 24 to 45 years (average 34 years). The duration of diabetes ranged from 7 to 32 years (average 20 years).

The 23 nondiabetic subjects were doctors, nurses, and laboratory personnel in the hospital. All were in good health with no evidence of infection or demonstrable kidney disease. Their age ranged from 19 to 41 years (average 30 years).

METHODS

Determinations were done on both mucoprotein and total serum protein precipitates. The mucoprotein fraction was precipitated from the perchloric acid soluble proteins of serum by the addition of phosphotungstic acid according to the directions of Winzler, Devor, Mehl and Smith.[14] The total serum protein precipitate was prepared by making a 1:10 dilution of serum, followed by precipitation of 0.5 ml. in 10 ml. of absolute ethanol.

The hexosamine determination was made by a modification of the Elson-Morgan procedure as described by Shetlar.[15] Optimal conditions were ascertained for each step of the procedure following reports of Blix[16] and Schloss.[17] The reaction was uninfluenced by variations in serum glucose concentration. The precision was ± 2 per cent.

Non-hexosamine carbohydrates were determined by Loewus'[18] modification of the anthrone method for polysaccharides. The concentration was calculated on the basis of a standard curve made by using mixtures of equal parts of galactose-mannose. Although later work has shown that the total serum protein contains sufficient tryptophan to affect the final value by about 10 per cent,[19] the values herein reported are not corrected since all were done under the same conditions and the tryptophan effect is relatively constant. The precision ranged from ± 1 to ± 2.5 per cent.

Protein determinations were made by a modification of the biuret method described by Weichselbaum.[20] A purified serum albumin preparation was used as a standard reference, and thus the values are correspondingly higher than those based on pooled normal serum as a reference.

RESULTS

The distribution and the mean values of the results for the various determinations made on the total serum protein and mucoprotein precipitates are given in figures 1 and 2. These figures show graphically the relationships of the results obtained in each group of subjects to those obtained in each of the other groups.

Total Serum Protein Precipitate

As shown in figure 1, the total serum protein concentration was significantly* decreased in all of the diabetic groups and showed the greatest decrease in patients with nephropathy. The concentration of the *non-hexosamine* constituent increased in all the diabetic cases with, again, the greatest change occurring in the patients with nephropathy. Although there was no significant difference in results obtained in Groups D-1, D-2, D-3 and D-4, there was a significant difference between the results in nondiabetics and diabetics without complications (group D-1) and an indication of an additional increase in diabetics with nephropathy (group D-4) over the other diabetic groups. While the same general trend of an increase in total serum protein-bound *hexosamine* occurred in all the diabetic groups, the significant differences were found between the nondiabetics (N) and diabetics without complications (D-1) ($p < 0.05$) as well as between nondiabetics and diabetics with retinopathy and nephropathy (D-4). Although there was a marked increase in observed values for diabetics with minimal retinopathy (D-2) which was significantly different from the normals, this increase was not sufficient to be statistically different from Group D-1 at a level of $p = 0.05$. No significant difference was found between group D-3 and group D-4. While the same general trend of an increase in total serum protein-bound *hexosamine* occurred in all the diabetic groups, the significant differences were found between the nondiabetics (N) and diabetics without complications (D-1) and between group D-1 and diabetics with minimal retinopathy (group D-2). No significant difference was found between group D-3 and group D-4.

Mucoprotein Precipitate

All three determinations done on the mucoprotein fraction, protein, hexosamine, and non-hexosamine carbohydrate showed the same general pattern of increase in the diabetic groups over the nondiabetic. Here, too,

*Wherever the term "significant" is used, unless otherwise stated, the groups are statistically different as indicated by the *t*-test at the level of $p \leqq 0.01$.

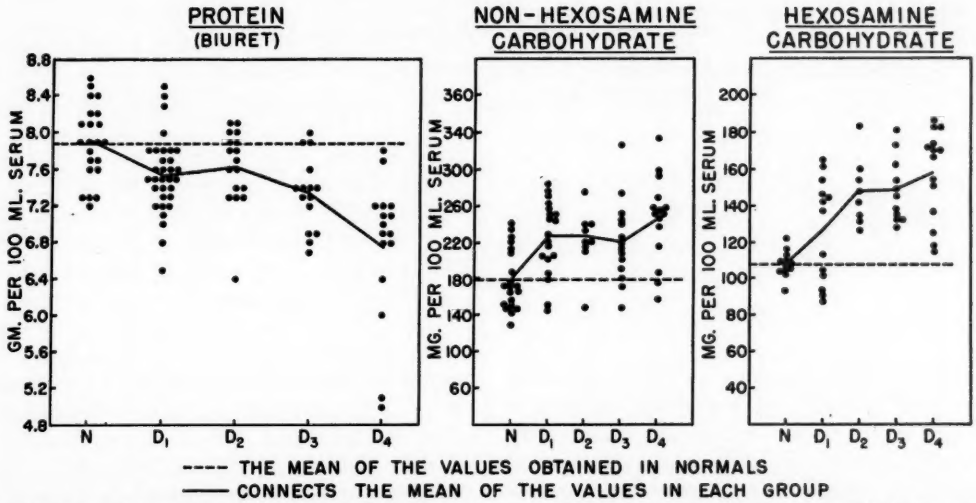

FIG. 1. The total protein and protein-bound carbohydrate in the serum of normals and of diabetics. N Nondiabetics. D-1 Diabetics without complications. D-2 Diabetics with minimal or moderate retinopathy without nephropathy. D-3 Diabetics with marked retinopathy without nephropathy. D-4 Diabetics with retinopathy and nephropathy.

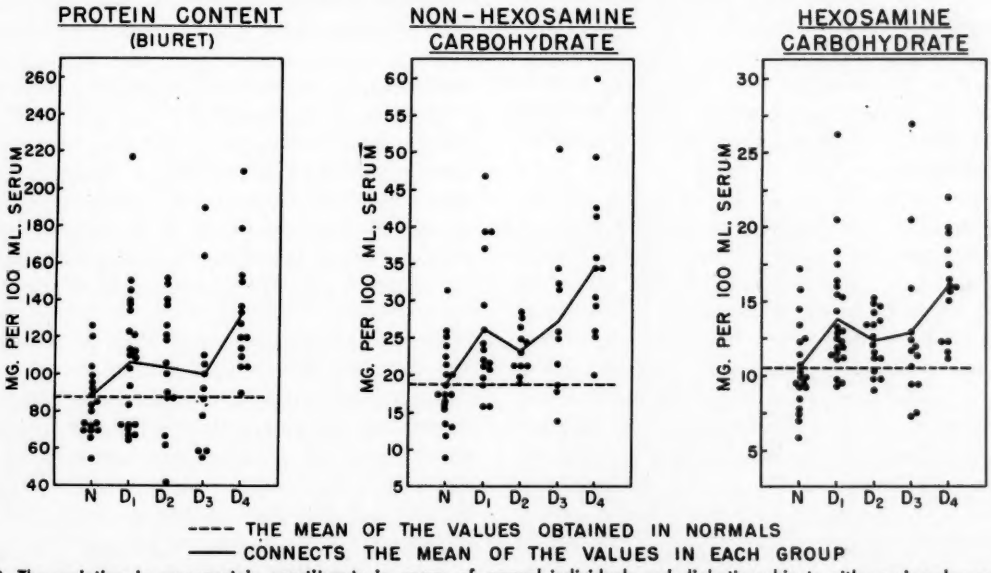

FIG. 2. The variation in mucoprotein constituents in serum of normal individuals and diabetic subjects with varying degrees of complications. (For criteria of classification see legend of figure 1.)

it is noticeable that diabetics without complications (D-1) and diabetics with various degrees of retinopathy but without nephropathy (D-2 and D-3) vary little from each other, but that there is a significant difference between the nondiabetics and the diabetics without complications (D-1). There is also a significant difference ($p < 0.05$) in results between diabetics with and without nephropathy (D-4 and D-3), particularly in measurements of the protein content and non-hexosamine content of the mucoprotein fraction.

DISCUSSION

The pattern of variation in total protein concentration here reported is closely parallel to that found by Nielsen

TABLE 1

Serum concentrations of protein-bound carbohydrate

Groups*	Total serum protein precipitate					Mucoprotein precipitate				
	Protein		Non-hexosamine carbohydrate		Hexosamine	Protein		Non-hexosamine carbohydrate		Hexosamine
	(gm. per 100 ml.)		(mg. per 100 ml.)			(mg. per 100 ml. serum)				
	MEAN	S.D.	MEAN	S.D.	MEAN	MEAN	S.D.	MEAN	S.D.	MEAN S.D.
N	7.89	± 0.40	178	± 33	108 ± 7	85	± 19	18.8	± 5.5	10.6 ± 3.3
D-1	7.54	± 0.35	224	± 40	126 ± 27	108	± 34	26.5	± 9.1	13.8 ± 2.8
D-2	7.62	± 0.54	224	± 33	147 ± 17	103	± 31	23.5	± 3.1	12.3 ± 1.9
D-3	7.34	± 0.40	220	± 45	148 ± 17	100	± 43	27.2	± 10.1	13.0 ± 3.3
D-4	6.76	± 0.67	245	± 46	158 ± 24	132	± 30	35.0	± 10.9	16.1 ± 3.3

*For criteria of classification see legend of figure 1.

and Poulsen.[12] As these authors, as well as Schneider, Lewis and McCullagh,[21] have pointed out, the drop in total protein concentration is due mainly to a fall in the albumin component. It is of interest that the first indication of this fall comes in diabetics without complications or with minimal retinopathy and before the development of proteinuria. These changes in total protein probably indicate a disordered pattern of protein metabolism in the diabetic as a result of poor control.[21]

The protein-bound non-hexosamine carbohydrate concentration in this study was definitely increased even in the diabetics without complications. This is the main point of difference between our data and those of Nielsen and Poulsen and of Berkman, Rifkin and Ross. There is some additional increase in this component with the appearance clinically of nephropathy, and all three groups of workers agree that a definite increase over that of the nondiabetic is associated with clinical evidence of vascular changes as shown by the appearance of retinopathy.

Our results on total protein-bound hexosamine concentrations were quite parallel with those of the two groups of workers mentioned above. The results of this determination showed a definite increase in concentration of the protein-bound hexosamine in the diabetics without complications (D-1) over that found in nondiabetics (N). In addition there was a further increase in concentration of this substance found in the sera of diabetics with minimal or moderate retinopathy (D-2); and, as may be observed in figure 1, the next evidence of any increase comes in the values found for the hexosamine in the serum of diabetics having nephropathy as well as retinopathy (D-4).

In the work on the mucoprotein fraction reported herein, there is the same general pattern noted as with the total protein-bound carbohydrate. That is, there is an increase in all diabetics with an additional increase in those with evidence of nephropathy. The principal difference between our data and those of Berkman, Rifkin and Ross is again found in the diabetics without complications. We find a definite increase in concentration of the components of the fraction in diabetics without complications (D-1) as compared to the nondiabetics (N), while they find an increase in concentration only after the appearance of vascular change as indicated by retinopathy. Both groups then find some additional increase in concentration with the appearance of nephropathy.

Increases in concentration of serum protein-bound carbohydrate have been reported in a variety of diseases such as chronic infections,[22] neoplasms,[9, 23] nephritis,[24] lupus erythematosus disseminatus,[25] rheumatic fever,[26] and scurvy.[6] In many of the reports a parallelism is noted between the degree of increase and the degree of cellular alteration, but it is also noted that the excess of carbohydrate material is related to different fractions of the serum in the various diseases where such analyses have been done. An attempt has been made by Pirani and Catchpool[6] to establish a causal relationship between protein-bound carbohydrate material in serum and alterations within the tissue in experimental scurvy. These authors suggest that there is a direct relation between the amount of mucoprotein in serum and the degree of depolymerization of the ground substance of connective tissue in the scorbutic animals.

Very little is known about the chemical nature of the components measured in any of the above studies.[27] It is probable that the protein-bound carbohydrate exists as polysaccharide complexes combined with some of the serum proteins, and it has been shown that the amount of carbohydrate bound to the different serum proteins varies considerably.[22, 29, 30] Some of the best defined carbohydrate-protein complexes and probably some of the proteins with the highest carbohydrate-protein ratio are found in the Winzler fraction. In this connection, it is

of interest to note that in group D-4, the group with the greatest degree of vascular complications, approximately 25 per cent of the increase in the total protein-bound carbohydrate is due to the increase in the mucoprotein fraction.

The variation in concentration of the total protein-bound carbohydrates reported might be due to variation in the composition of the serum proteins with an increase in concentration of carbohydrate-bearing proteins as a result. Some speculation has arisen as to the possibility that increases in the protein-bound carbohydrate in diabetics may be due to the increase in the alpha-2 globulin fraction reported in diabetics with intercapillary glomerulosclerosis by Rifkin and Petermann[31] and found in this laboratory.[32, 33] The alpha-2 fraction of serum is reported to have a high content of protein-bound carbohydrate.[34] Although from experience in this laboratory[30, 32] there is reason to believe that the concentration of protein-bound carbohydrate is principally influenced by an increase in the alpha-2 globulin fraction in the group of diabetics with the most marked complications, no such explanation can be given for the other groups.

The possibility that changes in the amount and composition of the carbohydrate bound to a serum protein might occur is indicated by Greenspan and his associates[35] who reported changes in the carbohydrate-protein ratio of the mucoprotein fraction of serum from patients with certain liver diseases. From the present data, such a possibility could not be evaluated since the data were insufficient to interpret the changes noted in hexosamine-non-hexosamine carbohydrate ratio or in the carbohydrate-protein ratios.

Although it has been reported[7] that in diabetes a correlation exists between the level of blood glucose and the level of protein-bound carbohydrates, neither we nor Nielsen and Poulsen nor Berkman have been able to confirm this correlation. In fact, Nielsen and Poulsen also attempted to correlate sugar excretion in the urine for the preceding two or three days and the protein-bound carbohydrates and could not find any relationship. Furthermore, preliminary work with paper chromatography indicates that little or no glucose was found as a constituent of the protein-bound polysaccharides.

Thus, in conclusion, it may be said that changes in the concentration of protein-bound carbohydrate of serum seem to be related to many different pathologic conditions and may be a reflection of different alterations within the serum protein fractions or within the carbohydrate-containing protein itself. It will therefore be necessary to investigate in more detail the nature of the increase in protein-bound carbohydrate in the serum of diabetics before any closer relationship can be established between these substances and the vascular complications of diabetes.

SUMMARY

1. A study has been made of the changes in total serum protein and serum protein-bound carbohydrate and in the mucoprotein fraction from serum in 81 diabetics and 23 nondiabetics.

2. It was shown that:

a. The serum protein values decrease significantly in all groups of diabetics including those without complications (D-1) compared to values found in nondiabetics (N).

b. A general increase in concentration of the non-hexosamine and hexosamine components of a total serum protein precipitate and of a mucoprotein fraction of serum takes place in the sera of diabetics without complications (D-1) compared to that found in nondiabetics (N).

c. The results found in three groups of diabetics, without complications (D-1), with minimal or moderate retinopathy (D-2), and with marked retinopathy but without nephropathy (D-3), showed no essential differences between the groups with one exception. The total serum protein-bound hexosamine concentration was found to be increased over that of the nondiabetic (N) in the serum of diabetics without complications (D-1), with a second increase in concentration found in the diabetics with minimal retinopathy (D-2).

d. An increase in concentration of both the non-hexosamine and hexosamine components of the protein precipitates is shown in diabetics with nephropathy (D-4) over the concentrations found in the serum of diabetics with marked retinopathy but without nephropathy (D-3).

3. The implications of the increases in the concentration of the polysaccharide components of serum are discussed.

ACKNOWLEDGMENT

We are indebted to Miss Anna Gotsis for valuable technical assistance and to Dr. Alexander Marble for advice and encouragement throughout this investigation and for his assistance in the preparation of this manuscript.

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SUMMARIO IN INTERLINGUA

Hydrato de Carbon Ligate a Proteina in le Sero de Patientes Diabetic con e sin Complicationes Vascular

1. Esseva executate un studio del cambiamentos in le proteina total del sero e le hydrato de carbon ligate al proteina seral e in le fraction de mucoproteina del sero in 81 diabeticos e 23 subjectos nondiabetic.

2. Le sequente constatationes esseva facite: (a) Le valores pro proteina seral decresce significativemente in omne gruppos de diabeticos in comparation con le nondiabeticos. Isto es ver etiam pro le gruppo de diabeticos sin complicationes.

(b) In le sero de diabeticos sin complicationes, il occurre in comparation con le nondiabeticos un augmento general del concentration del componentes nonhexosaminic e hexosaminic de un precipitato del proteina total del sero e de un fraction mucoproteinic del sero.

(c) Le resultatos obtenite in tres gruppos de diabeticos — le gruppo sin complicationes, le gruppo con minime o moderate retinopathia, e le gruppo con marcate retinopathia sed sin nephropathia — exhibiva nulle differentias essential intergruppal. Il habeva un exception de iste regula. Le concentration del hexosamino ligate al proteina total del sero monstrava — in comparation con le gruppo del nondiabeticos — un certe augmento in le gruppo del diabeticos sin complicationes e un augmento plus considerabile in le gruppo del diabeticos con minime retinopathia.

(d) Un augmento del concentration tanto del componentes nonhexosaminic como etiam del componentes hexosaminic del precipitatos proteinic esseva demonstrabile in le gruppo del diabeticos con nephropathia in comparation con le gruppo del diabeticos con marcate retinopathia sed nulle nephropathia.

3. Es discutite le implicationes del augmentos in le concentration del componentes polysaccharidic del sero.

Governmental Regulation of the Food Industry

The Federal Food and Drug Administration is the agency responsible for enforcing the Food, Drug and Cosmetic Act of 1938, as it was for the preceding law enacted in 1906. It is of prime significance from the standpoint of public relations that each of these laws in turn has often been referred to in common parlance as the "Pure Food Law."

. . . . American food industry as a whole was quick to recognize that a sanely administered pure food law would not only protect the public but also safeguard the best elements of industry against unscrupulous competition by the worst elements. Relations between food industry and food officials have grown steadily more cordial and for years have presented an unusual degree of harmony between the policeman and the policed. This has been invaluable in making food law effective and would have been impossible if the breath of scandal and corruption had ever entered the Food and Drug Administration service.

One must hasten to deny, however, that there are no disputes or dissensions. The food industry presents very large and diversified interests, and the multiplicity of opportunities for conflict is great. Hence, sharp litigation often occurs in the courts, and charges of bureaucracy are not infrequently made. Thousands of other questions are, however, successfully settled out of court in reasoned adjustments.

The Food and Nutrition Board of the National Research Council had a very different genesis. It came into being in 1940 in the midst of a period of very active research in the field of nutrition. This research had made it clear that the nutritional needs of man, contrary to earlier accepted opinion, are actually very complex. Pronounced nutritional diseases, such as beriberi, pellagra, rickets, scurvy, and xerophthalmia, occurring by accident throughout the world, through misfortunate food habits or restrictions, were clearly due to substances lacking in certain dietaries. For the first time, we knew what the deficiencies were, and it was abundantly clear that it is easy to go wrong in choosing one's food even though no question of toxic impurities is involved. The chief emphasis of the Food and Nutrition Board has, accordingly, been on adequacy of food from the nutritional standpoint.

In spite of this contrast of approach, fruitful co-operation has developed between the Food Administration and the Board. This co-operation began at the time of the Board's birth when the Administration announced hearings on vitaminized white flour, out of which grew what we now know as enriched flour.

A narrow view of its responsibilities might easily have led the Administration to disavow responsibility for helping to make the prevailing diet more adequate. The position might well have been taken that the Administration's sole job is to insure that the food supply is pure and not misrepresented with regard to identity or quality. To that fact that a broader view was taken is due the developing use of the law to insure that food is adequate as well.

From "Purity and Adequacy of Foods" by Robert R. Williams, Chairman of the Committee on Definitions and Standards of Identity of Foods, Food and Nutrition Board, National Research Council, in *Science* 120:473-75, Sept. 24, 1954.

Diabetes in a Neuropsychiatric Hospital

Otto F. Ehrentheil, M.D., Bedford, Massachusetts*

In February 1952, a special diabetic ward was established in the United States Veterans Administration Hospital at Bedford, Mass. In the more than two years that this ward has been in existence, its advantages in the management of psychotic diabetics have become evident. Since no report regarding such a special ward has been published, the experiences in Bedford may be of general interest.

DIABETIC CASE FINDING

The steps followed in the detection of cases are as follows:

1. Every patient in the hospital has at the time of admission and at least once a year a complete physical check-up, including a urine examination.

2. The weight of every patient is checked every month and charted on a graph, so that any unusual weight loss is readily discovered.

3. For any kind of acute illness the patient is brought to the medical-surgical service, where a thorough examination is done, of course including a urine examination.

If glycosuria is found, the same diagnostic procedures are done as are generally employed for the establishment of the diagnosis of diabetes mellitus.

FREQUENCY OF DIABETES

An examination of the frequency of diabetes in a neuropsychiatric hospital is of particular interest because there are a number of papers in the literature dealing with the relationship of carbohydrate metabolism and psychic conditions. Table 1 shows the male diabetic patients of our hospital grouped according to age and psychiatric diagnosis.

It is seen from this table that the diabetics amount to 2.2 per cent of the total male patients, an incidence which is not statistically significantly different from that in the general population as found in the survey in Oxford, Mass.,[1] and similar surveys in Canada.[2, 3] The same holds true of the frequency among the schizophrenic patients as compared with the general population.

TABLE 1
Diabetic patients according to age and psychiatric diagnosis

Age (years)	18 to 34	35 to 44	45 to 54	55 to 64	65 and over	Totals
Schizophrenia						
Paranoid type	0	0	3	9	0	12
Catatonic type	0	2	0	3	0	5
Hebephrenic type	0	0	1	4	0	5
Simple type	0	0	0	3	0	3
Other types	0	0	1	0	1	2
Total schizophrenia	0	0	5	19	1	27
Chronic alcoholism with psychotic reaction	0	0	0	3	0	3
Syphilis with psychotic reaction	0	0	0	4	0	4
Organic lesion with psychotic reaction	0	0	0	0	0	0
Affective psychosis	0	0	0	3	1	4
Miscellaneous	0	0	0	1	0	1
Total diabetics	0	2	5	30	2	39
Total male patients	492	273	229	698	119	1811

MANAGEMENT OF A SPECIAL DIABETIC WARD

Every physician treating diabetics in the general population knows that many patients like to "cheat" in their diet, especially after the anxiety of the first few months following the diagnosis of diabetes has passed. It is easy to understand that this behavior becomes a serious problem when the patients have no insight into their diabetic condition. It was our experience in this hospital that diabetic patients kept on a diabetic diet, but living among patients who received a regular diet, were jealous, complained bitterly, or were stealing food from the trays of other patients. Patient H. S. illustrates this point. He believed that "the whole story about my diabetes is a fake," that physicians, dietitians, and nurses were deceiving him and not giving him the sugar that by right belonged to him, and were selling the sugar in the black market. He stole food during the time he was

From the United States Veterans Administration Hospital, Bedford, Mass.

*Senior Physician, Medical-surgical Service.

stationed on the general semi-infirmary ward.

From the beginning of the establishment of the diabetic ward, the same menu was given to every patient. The amount of carbohydrate, protein, and fat is of course different and varies according to the metabolic needs of the patient and the insulin given to him, but the kind of food is the same for everyone on the ward. A difficulty that has not been completely overcome is that a number of our patients are allowed the freedom of the hospital and its grounds and therefore have access to the canteen, where they are able to buy extra food. In general, it is believed that the psychiatric gain resulting from giving patients ground privileges surpasses the harm of deviations from accurate diabetic management. One rule, however, is impressed on the patients and enforced by the psychiatric aides; namely, that food, especially sweets, may not be brought into the ward.

Four standardized diabetic diets (the same food, varying only in amount) are used on the ward as follows:

TABLE 2

Diet	Carbohydrate	Protein	Fat	Total Calories
I	150 gm.	90 gm.	80 gm.	1680
II	200 gm.	90 gm.	80 gm.	1880
III	250 gm.	100 gm.	80 gm.	2120
IV	300 gm.	100 gm.	100 gm.	2500

This gives enough flexibility for diabetic management and makes the work for the dietitian, the kitchen personnel, and the aides easier than if a number of individual diets were prescribed. Two patients on the ward, one a manic-depressive, and the other a schizophrenic paranoid, both in excellent contact and strictly obeying the rule against bringing food into the ward, are allowed to go to the main dining hall and there eat a regular diet. The sugar metabolism of these two patients has to be controlled with greater amounts of insulin.

The insulin used on the ward is mostly globin insulin and is given at 7 a.m. This type of insulin with prolonged action of intermediate degree was preferred to protamine zinc insulin, since it was thought that there would be less risk of insulin reactions during the night. It was feared, especially when treating catatonic or other withdrawn psychotics, that an insulin reaction could easily be overlooked during the sleeping hours. Such patients will not talk and will not complain. With a type of insulin having its maximum effect in the afternoon, an insulin reaction will be more readily discovered. In only two cases in which high fasting blood sugar values continued during treatment with globin insulin was an additional small dose of protamine zinc insulin given.

A special diabetic ward facilitates the establishment of a nursing routine for the care of psychotic diabetics. Such routine procedures include a urine examination three times a day before meals on all new and all poorly controlled patients. These tests are made by nurses and aides. In well controlled cases, a test of urine is made on only one day during the week, but on this day before each meal. Tests for acetone are done on urine specimens showing a 2 plus reaction with Clinitest indicating approximately 0.75 per cent of sugar. Once a week, the urine specimens are sent to the clinical laboratory for testing, and once a month a fasting blood sugar test is made in every case. Oral glucose tolerance tests with 100 gm. of glucose and intravenous glucose-tolerance tests are performed when needed. In the latter tests, 0.5 gm. of glucose per kg. of body weight is administered in a 20 per cent solution, and the drop infusion is so regulated that the entire amount is given in exactly 30 minutes. Blood specimens are taken before starting the infusion and half an hour, one, two, and three hours after its completion.

Nurses and aides are alerted to look for any disease of the feet. The patients receive shower baths twice a week and foot soaks on two other weekdays. On these occasions, the feet are always inspected. Cases of epidermophytosis are carefully treated, as are plantar callosities. Toenails are clipped by the aides and not by the patients themselves. After the shower baths or foot soaks, the feet of every patient are treated with a fungicidal powder. Buerger's exercises are attempted with all patients. The co-operation of even quite regressed and negativistic patients is surprisingly good if such exercises are done in groups of about 15 patients. From time to time the ward physician conducts special foot rounds, checking not only the color and temperature of the feet and the presence or absence of epidermophytosis but also the pulsations in the dorsal pedal and posterior tibial arteries. Wherever indicated, skin temperature readings and oscillometer studies are done by the Physiotherapy Department.

The ward is small and has a capacity of only 30 beds. Because of the limited space the remaining nine diabetics have to be cared for on other wards. These patients either have mild diabetes or are so mentally disturbed that they have to be kept on the acute psychiatric ward.

PSYCHOTIC PATIENTS WITH TEMPORARY COMPLETE REMISSION OF DIABETES

The fact that many patients in neuropsychiatric hospitals remain in the hospital for many years and have frequent laboratory tests provides an opportunity to fol-

low the course of their diabetes more closely than possible under ordinary circumstances. In the course of these studies three patients were found who presented an almost complete remission. According to the laboratory findings some years ago, these same patients were considered to have moderately severe diabetes. Since such improvements in the course of diabetes are still regarded as unusual, these three cases are briefly reported.

Case 1

This patient, D.M., was 54 years old. His father and one brother had been hospitalized for mental illness, but no diabetes had occurred among blood relations. The patient was first hospitalized for several months in 1923, when he reported that he was seeing small animals, and various grotesque figures. Between 1927 and 1943, he was in and out of mental hospitals several times, until in 1943, he was discharged in full psychiatric remission. He then worked for three years, during which time he had considerable family troubles. His mental symptoms recurred in 1950 and he began to drink. He had hallucinations and paranoid ideas and engaged in several arguments with his eldest son (his guardian), whom he accused of taking his money. (This accusation turned out to be correct.) He was drinking heavily at that time. When he was admitted on Aug. 9, 1950, he was somewhat disturbed and had auditory and visual hallucinations. The diagnosis was schizophrenic reaction, unclassified, chronic, severe.

The urine on admission contained sugar graded 4 plus. On the eighth hospital day the fasting blood sugar was 150 mg. per 100 cc. Results of a glucose tolerance test performed September 1 gave the following results:

		Blood sugar mg./100 cc.	Urine sugar
Fasting		182	4 plus
After 100 gm. of glucose:	½ hour	221	4 plus
	1 hour	260	4 plus
	2 hours	299	4 plus
	3 hours	260	4 plus

His diabetes was controlled by diet (C-200, P-80, F-60) alone.

Between Sept. 1950 and Feb. 1952, the fasting blood sugar was examined monthly. While the findings on Sept. 2 and Oct. 6, 1950, were high (140 and 204 mg. per 100 cc. respectively), the next monthly values were all normal until July 3, 1951, when the fasting blood sugar was 198 mg. The next three monthly findings were normal. On Nov. 19, the fasting blood sugar was 133 mg. and on Dec. 17 it was 141 mg. Since then all the monthly fasting blood sugars have remained normal (to March 1953). It is to be emphasized that during all this time the patient never received insulin. Since Feb. 1, 1952, he has been on a diet of C-250, P-90, F-80, and has excreted no sugar. An oral glucose-tolerance test done on March 7 of that year with 100 gm. of glucose showed the following:

		Blood sugar mg./100 cc.	Urine sugar
Fasting		73	0
After 100 gm. of glucose:	½ hour	136	0
	1 hour	112	0
	2 hours	97	0
	3 hours	77	0

Another oral glucose-tolerance test on April 24, after the patient had been on a very rich diet (against advice), showed an entirely normal curve; on May 3 the results of an intravenous glucose tolerance test were also within normal limits.

A glucose tolerance test done on March 17, 1953, after the patient had been on an unrestricted diet for 11 months and had put on considerable weight, gave the following results:

		Blood sugar mg./100 cc.	Urine sugar
Fasting		91	0
After 100 gm. of glucose:	½ hour	131	0
	1 hour	182	1 plus
	2 hours	121	0
	3 hours	88	0

Discussion

This case is presented because the laboratory tests at first revealed moderately severe diabetes. The diabetes was brought under control easily by dietary treatment alone. From then on the fasting blood sugar values were mostly normal, although sometimes for no apparent reason the fasting blood sugar was high. In August 1950 the body weight was 150 lb., compared with 124 lb. in March 1952 when the patient was on the diabetic ward. It is well-known that decreasing weight will ameliorate a diabetic condition. However, it is questionable whether the change observed in this patient can be explained entirely in this way. Other factors, such as the excessive consumption of alcoholic drinks just before readmission and the emotional turmoil at that time, may have contributed to the change.

Case 2

This patient, J. M., was 58 years old. The family history was negative, except that his mother was somewhat unstable emotionally. In the summer of 1930 the patient began to stutter, had memory defects, began to have difficulties with his gait, and fell several times. His behavior became childish. After admission on Feb.

7, 1931, blood and spinal fluid tests reported a positive Wassermann reaction and the colloidal gold curve was 5555321000. There were some neurologic findings and temporal pallor of both disks. On March 9 the patient had hallucinations and delusions. On March 30 he became practically mute. He was diagnosed as having meningoencephalitis syphilitica with psychotic reaction. Antisyphilitic treatment was given from 1931 to 1934 (neoarsphenamine and tryparsamide). In October 1934 he had malaria therapy. Since then he had received no antisyphilitic therapy because the laboratory findings had become completely negative.

On Feb. 2, 1948, the urine contained sugar graded 4 plus. Eight days later a glucose tolerance test showed the following:

		Blood Sugar mg./100 cc.
Fasting		166
After 100 gm. of glucose:	½ hour	241
	1 hour	294
	2 hours	250
	3 hours	307

The patient was put on a rather liberal diabetic diet and from then on rarely had sugar in his urine. The monthly fasting blood sugars were normal during these years except for July 1951, when the value was 140 mg. A glucose tolerance test on April 2, 1952, gave the following results:

		Blood sugar mg./100 cc.	Urine sugar
Fasting		102	0
After 100 gm. of glucose:	½ hour	134	0
	1 hour	98	0
	2 hours	83	0
	3 hours	80	0

Two intravenous glucose tolerance tests were given in April and May 1952. The blood sugar values were normal. After 10 months on a diet containing 300 gm. of carbohydrate an oral glucose tolerance test gave slightly increased values.

Discussion

This case presents a problem similar to the first one. Here again the patient had glycosuria and a typical diabetic glucose tolerance reaction, which reached a two-hour value of 350 mg. per 100 cc. The sugar metabolism was quickly brought under control by diet alone, and the monthly fasting blood sugar values from March 1948 to March 1953 were normal except for July 1951, when the value was 140 mg. On March 3, 1953, the glucose tolerance reaction was very slightly abnormal.

The weight curve of this patient is interesting. He had been overweight in 1947 and 1948. At the time of the glucose tolerance test which was typical of diabetes (1948) his weight was 202 lb. He later lost weight and was underweight in 1950 and 1951 (138 lb.). During 1952, while on the diabetic ward, he had a flat weight curve of 150 lb. This is approximately the normal weight for his height and age. Whether the decrease in weight alone explains the difference in the outcome of the glucose tolerance test is highly questionable. This patient is practically mute, and emotional disturbances may not be verbally expressed and therefore go unnoticed. The great fluctuations in his weight curve, which also are unexplained, may be related to changes in his emotional life.

Case 3

This patient, J. E. C., was 59 years old. Neither mental illness nor diabetes was found among blood relations. In 1933 the patient had hyperthyroidism, psychoneurosis, and chronic catarrhal otitis media. For several years he developed strange ideas. In 1939 he called the police asking protection against a gang which he believed was after him. He was admitted to Westboro State Hospital on May 26, 1939, where he was restless and noisy and had auditory and visual hallucinations. He was diagnosed as having dementia praecox, paranoid type, and was transferred to this hospital on Nov. 15. On admission physical examination revealed an operative scar from thyroidectomy and auricular fibrillation. Throughout the thirteen years in this hospital he was very deluded and withdrawn; sometimes he expressed grandiose ideas, and at times he was hallucinated. The diagnosis was schizophrenic reaction, paranoid type.

In July 1947 the urine contained sugar graded 2 plus; on Nov. 1, 1950, 3 plus sugar; and on the following day 4 plus sugar. On Dec. 13, an oral glucose tolerance test gave the following results:

		Blood sugar mg./100 cc.	Urine sugar
Fasting		163	2 plus
After 100 gm. of glucose:	½ hour	206	4 plus
	1 hour	235	4 plus
	2 hours	260	4 plus
	3 hours	270	4 plus

After this the patient was placed on a diet and given 20 units of NPH insulin. He remained on this regime for one year, showing 2 plus sugar only once. After he was transferred to the special diabetic ward, his insulin dosage was first decreased to 15 units of globin insulin daily. From April 1952, until Nov. 10, 1952, he received only 10 units daily. From then on no insulin

was given. The monthly blood sugar values were normal during this time. The urine, which was examined three times a day while the patient was on the special ward, occasionally gave a 1 plus reaction. Throughout this period the patient was on a diet of C-200, P-90, F-80. A glucose tolerance test done on March 3, 1953, had the following results:

	Blood sugar mg./100 cc.	Urine sugar
Fasting	90	0
After 100 gm. of glucose: ½ hour	141	0
1 hour	139	1 plus
2 hours	108	1 plus
3 hours	88	1 plus

Discussion

This patient has shown occasional sugar in his urine since 1947. In November and December 1950 the glycosuria was greatly increased and the glucose tolerance curve indicated moderately severe diabetes. After almost two years of treatment with small and diminishing doses of insulin the patient was treated by diet alone and the blood glucose tolerance was completely normal. The weight in 1946 averaged 156 lb., but in December of that year it rose to 166 lb. In July 1947, when sugar was found for the first time, it was 170 lb. He then lost weight again and in December 1950 weighed only 150 lb. In 1952 while on the diabetic ward his weight hovered around 136 lb. In February 1951 he had a purulent otitis media. Since he had ear trouble in 1933 and 1940 he may have already had a low-grade infection in December 1950, and this may have had a damaging effect on the sugar metabolism. However, the difference between the greatly abnormal glucose tolerance value in December 1950 and the perfectly normal glucose tolerance value in March 1953 shows that either a remarkable remission has taken place or that the sugar regulation was easily disturbed by the ear infection.

All three of these cases exhibited the typical laboratory findings of moderately severe diabetes, followed by normal glucose tolerance values. The tests were repeated on two of the patients after they had been on an unrestricted diet for many months. The curves became very slightly abnormal, but far less than when the diabetes was first recognized. Only in case 1 does it appear from the psychiatric record that the patient was in a much more acute psychiatric and emotionally disturbed state at the time of the diabetic findings than at the time of the diabetic remission. In the two other cases no such deductions can be drawn. The influence of obesity and infection was considered.

The fact that among 39 diabetic patients in this hospital, three such cases could be found which had, at least temporarily, a complete remission suggests that such a course may not be as unusual as is commonly believed, at least not among psychotic patients. Joslin[4] states: "Remissions of the disease (diabetes) are common when the exciting cause for onset is removed and prompt aggressive treatment, soon after the onset of diabetes is recognized, is instituted particularly in children, and this often drives it into hiding." The patients reported here are adults in their fifties.

The results of these investigations on the special diabetic ward have implications for the diagnosis, treatment, and especially prognosis of diabetes in psychotic patients.

SUMMARY

1. The frequency of diabetes in the Veterans Administration Hospital in Bedford, Massachusetts, is statistically not significantly different from that in the general population.

2. The management and the advantages of a special diabetic ward in a neuropsychiatric hospital are discussed.

3. Three cases are presented in which typical laboratory findings of moderately severe diabetes were followed by complete or almost complete remission.

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SUMMARIO IN INTERLINGUA

Diabete in un Hospital Neuropsychiatric

1. Le frequentia de diabete al Hospital Bedford, Massachusetts, del Administration de Veteranos non differe de maniera statisticamente significative ab illo del population general.

2. Le gerentia e le avantages de un sala diabetic special in un hospital neuropsychiatric es discutite.

3. Es presentate tres casos in que typic constatationes laboratorial de formas moderatemente sever de diabete esseva sequite per complete o quasi complete remissiones.

Recent Statistics on Diabetes*

The death rate from diabetes in the first nine months of 1954 was appreciably less than in the corresponding period a year ago (table 1). For the country as a whole, it was about 5 per cent less than in 1953, according to the returns in the 10 per cent sample of death certificates upon which these provisional statistics are based. A somewhat larger reduction was recorded in the death rate from the disease among the urban wage-earning population represented by persons insured under Industrial policies in the Metropolitan Life Insurance Company. Most of the decline occurred in the early months of the year.

The eastern seaboard states and cities, and the two Canadian cities from which the statistics are regularly received, all experienced a decrease in diabetes death rates in the first nine months of 1954 as compared with the same period of 1953.

Data for England and Wales show a sharply lower mortality from diabetes in 1954 as compared with 1953. This is shown by the figures for London Administrative County for nine months and for the whole country for the first quarter of the two years. The outbreak of respiratory diseases early in 1953, which was largely responsible for the relatively high mortality recorded during that period, was much more severe in England than in this country. Consequently, the relative reduction in diabetes mortality was greater for England than for this country. Nevertheless, the rate for 1953 as a whole, in England and Wales, was somewhat less than in 1952. The decline was about 5 per cent for the total population and differed little by sex.

For the first six months of 1954, 7 of the 9 geographic divisions of the United States experienced lower death rates from diabetes than in the corresponding period of 1953, according to provisional data based upon the 10 per cent sample. As table 2 shows, the decline was particularly large in the East and West North Central states. In most areas the death rates in the first half of 1954 were below the level of the first half of 1952 also.

Final mortality figures for the year 1952 for the United States show that there were 25,474 deaths ascribed to diabetes, corresponding to a rate of 16.4 per 100,000 population. These figures may be compared with 25,047 deaths and a rate of 16.3 per 100,000 population in 1951.

Provisional data for the United States for the entire year 1953 show a decline from 1952 in diabetes death rates in all color-sex groups except white males. Among them the increase was very small (table 3).

The provisional data by age, without distinction of color or sex, showed a decline in 1953 from 1952 in age groups 45 on, where the bulk of the mortality from the disease is concentrated (table 4). The death rates at the younger ages were higher than in the earlier year, but the number of deaths involved in the sample for most of these age groups was rather small. Final figures may show a somewhat different picture.

Complete mortality data from diabetes for the United States by sex, age and color, now available for 1951, are given in table 5. It is notable that at ages under 15 there were 198 deaths from diabetes, or less than 1 per cent of the total from the disease, and the death rate from the disease in this age group was less than 1 per 100,000. Among white persons the rate at ages 10-19 was higher among girls than among boys, but the figures then show no sharp differential by sex until after age 35. Between ages 35 and 49 the death rates for males were somewhat higher than among females. From then through old age the death rates for females were the higher; proportionately the differences were largest between 60 and 69. In the nonwhite population the death rates of females were consistently higher than those for males after age 30; the differences were relatively largest between ages 40 and 64. In all but one quinquennial age group in this span, the female rate was more than double that for males.

While in the aggregate the rates for the white population are higher than those for the nonwhite population, this does not hold uniformly in the several age groups. Among males up to age 70, and among females up to age 65 the rates are the higher in the nonwhite population, but beyond these ages the reverse is true. In all color-sex groups, with a few minor exceptions, the rates rise steadily throughout adult life, but show a fall after

*Submitted by the Committee on Statistics, Herbert H. Marks, Chairman. The Committee welcomes suggestions or actual material suitable for this section in future issues, from Association members and other readers of the Journal.

TABLE 1

Recent data on diabetes mortality: Deaths and death rates—January-June and January-September, 1954 and 1953

Area	Death rates per 100,000				Number of deaths			
	Jan.-Sept.		Jan.-June		Jan.-Sept.		Jan.-June	
	1954	1953	1954	1953	1954	1953	1954	1953
United States (10% sample)	15.3	16.0	15.8	17.0	1,830	1,896	1,254	1,332
Metropolitan Life Ins. Co. Industrial Policyholders	14.7	15.8	15.3	16.2	2,010	2,189	1,391	1,479
New York State	19.5	21.1	20.1	20.9	2,288	2,450	1,562	1,610
New York City	18.7	21.0	19.4	20.7	1,150	1,277	795	840
Maryland	16.3	16.7	16.3	17.4	309	313	205	216
Baltimore, resident	18.3	19.7	18.0	21.3	132	142	86	102
Boston	22.6	25.4	27.0	30.0	125	154	108	121
Philadelphia	27.7	29.8	30.0	29.8	445	475	320	315
Toronto	15.9	17.9	16.8	20.3	81	89	57	67
Montreal, resident	16.8	18.4	19.2	18.6	134	145	102	98
London (Administrative County)	7.0	8.2	6.8	9.4	175	206	113	157
	Jan.-Mar.		Jan.-Dec.		Jan.-Mar.		Jan.-Dec.	
	1954	1953	1953	1952	1954	1953	1953	1952
England and Wales								
Total	8.4	9.8	7.2	7.6	918	1,062	3,195	3,338
Males	6.2	6.8	5.0	5.2	325	356	1,066	1,091
Females	10.5	12.5	9.3	9.8	593	706	2,129	2,247

Rates for the states and cities are based upon local estimates of population. United States data based upon the returns from a 10 per cent sample of death certificates received in vital statistics offices, as published in *Current Mortality Analysis*, a monthly report of the National Office of Vital Statistics of the U. S. Public Health Service.

TABLE 2

Number of deaths and death rates from diabetes in geographic division; United States reporting area for the 10 per cent sample; January-June 1954, 1953 and 1952

Geographic division	Death rates per 100,000*			Number of deaths*		
	1954	1953	1952	1954	1953	1952
U. S. reporting area	15.8	17.0	16.6	1,254	1,332	1,276
New England	18.0	18.2	20.9	88	87	98
Middle Atlantic	22.1	23.2	23.1	342	356	356
East North Central	19.5	21.1	20.8	310	333	324
West North Central	15.1	18.4	17.5	109	131	126
South Atlantic	13.0	14.0	11.7	148	156	127
East South Central	10.9	8.9	10.7	63	51	63
West South Central	10.4	13.6	9.3	80	103	69
Mountain	7.1	12.0	14.6	20	33	38
Pacific	11.4	10.2	10.4	94	82	75

*Excludes armed forces overseas.

These data from the 10 per cent sample are subject to sampling error. The number of deaths, as given, does not cover the entire United States for each month but is limited by the completeness of the reporting area. The size of the reporting area is indicated by the footnote on page 7 of each monthly issue of the *Current Mortality Analysis*.

Source: Data furnished by National Office of Vital Statistics of the U. S. Public Health Service.

age 85 among white persons and somewhat earlier among the nonwhite.

The official population records of England and Wales have long been the best source of comprehensive data on mortality by occupation and socio-economic groups. Since 1851 these data have been assembled in that country in or about the decennial census year, except in 1941,

TABLE 3

Estimated deaths and death rates from diabetes by race and sex, United States, 1953 and 1952
(Based upon the returns from a 10 per cent sample of death certificates)

Race and sex	Death rates per 100,000*		Number of deaths*	
	1953	1952	1953	1952
Total				
Both sexes	16.0	16.2	25,390	25,250
Male	12.9	12.7	10,070	9,780
Female	19.1	19.6	15,320	15,470
White				
Both sexes	16.3	16.4	23,050	22,900
Male	13.3	13.1	9,330	9,050
Female	19.2	19.7	13,720	13,850
Nonwhite				
Both sexes	13.9	14.3	2,340	2,350
Male	9.0	9.1	740	730
Female	18.5	19.2	1,600	1,620

*Excludes armed forces overseas.

Source: Monthly Vital Statistics Reports—Annual Summary for 1953 & 1952, Part 2. National Office of Vital Statistics of the U. S. Public Health Service.

TABLE 4

Estimated deaths and death rates from diabetes by age, United States, 1953 and 1952
(Based upon the returns from a 10 per cent sample of death certificates)

Age groups	Death rates per 100,000*		Number of deaths*	
	1953	1952	1953	1952
All ages	16.0	16.2	25,390	25,250
Under 1	0.6	0.9	20	30
1-14	0.5	0.4	220	170
15-24	1.4	1.1	300	230
25-34	2.5	1.8	610	430
35-44	4.4	3.6	980	800
45-54	12.1	12.7	2,200	2,280
55-64	41.9	43.8	5,880	6,050
65-74	93.6	95.2	8,540	8,490
75-84	158.8	163.4	5,740	5,720
85 & over	120.5	148.7	880	1,010
Not stated			20	40

*Excludes armed forces overseas.

Source: Monthly Vital Statistics Reports—Annual Summary for 1953 & 1952, Part 2. National Office of Vital Statistics of the U. S. Public Health Service.

during the Second World War. Since the completion of the 1951 census of population, preliminary data of this kind have been published recently, based upon the deaths in 1950 and upon a 1 per cent sample of the population. (The Registrar General's Decennial Supplement, England and Wales, 1951 — Occupational Mortality — Part 1, London: Her Majesty's Stationery Office, 1954.) The publication gives the facts on men in the various socio-economic and occupational categories and for married women, classified according to the occupation of the husband. (In due course, the facts will be assembled covering the deaths in 1949 to 1953 which will be related to the census of population taken in 1951, the midpoint of the period.) For ages 20 to 64

TABLE 5

Number of deaths and death rates from diabetes by age, race and sex. United States, 1951

Age groups	Death rates per 100,000*					Number of deaths*				
	Total	White		Nonwhite		Total	White		Nonwhite	
		Male	Female	Male	Female		Male	Female	Male	Female
All ages	16.3	12.8	20.3	10.2	17.9	25,047	8,711	14,055	800	1,481
Under 1	0.4	0.5	0.4	—	—	13	8	5	—	—
1-4	0.4	0.4	0.5	0.3	0.4	60	25	29	3	3
5-9	0.3	0.2	0.4	0.6	0.5	47	13	25	5	4
10-14	0.7	0.4	1.0	0.7	1.0	78	18	48	5	7
15-19	1.1	0.6	1.2	1.9	2.1	111	28	57	12	14
20-24	1.4	1.1	1.4	2.6	2.3	154	51	72	15	16
25-29	2.2	2.2	2.0	2.8	2.8	268	118	113	17	20
30-34	2.2	2.2	1.9	2.5	4.6	258	111	104	14	29
35-39	3.1	2.9	2.2	6.7	8.9	352	146	113	37	56
40-44	4.8	4.6	3.4	6.5	17.8	504	213	162	33	96
45-49	8.6	7.4	6.8	13.1	30.2	794	309	286	59	140
50-54	16.6	12.9	15.9	23.0	54.5	1,397	490	611	88	208
55-59	30.8	23.5	34.2	37.8	71.0	2,277	796	1,175	110	196
60-64	57.6	41.2	71.9	45.5	98.5	3,558	1,185	2,085	95	193
65-69	86.0	63.3	108.3	65.3	94.3	4,394	1,442	2,627	128	197
70-74	119.9	93.5	148.2	65.1	109.7	4,310	1,472	2,607	84	147
75-79	154.7	124.1	186.7	85.1	124.2	3,411	1,185	2,087	57	82
80-84	177.0	153.2	207.9	52.6	110.0	2,115	760	1,291	20	44
85 & over	147.3	141.2	161.6	81.8	83.9	931	336	551	18	26
Not Stated						15	5	7	—	3

*Excludes armed forces overseas.

Source: National Office of Vital Statistics of the U. S. Public Health Service. Special Reports—National Summaries, Vol. 38, No. 11, Aug. 25, 1954.

the figures, presented in the form of a standardized mortality ratio, allow for differences in the age distribution of the separate classifications, but the figures for ages 65 and over relate simply to the proportion of deaths due to diabetes in these classifications. The social class groupings and the nature of the inclusions are:

Class 1	Professional, etc., Occupations
Class 2	Intermediate Occupations
Class 3	Skilled Occupations
Class 4	Partly Skilled Occupations
Class 5	Unskilled Occupations

Table 6 shows the facts both for all causes and for diabetes at ages 20 to 64. Among males the mortality from all causes of death was lowest in Social Class 2, next lowest in Social Class 4, about average in Social Class 1 and 3 and highest in Social Class 5. The mortality from diabetes, however, was lowest in Class 4, next lowest and slightly below the average in Social Class 2 and 3, next highest and somewhat above the average in Social Class 5, and highest in Social Class 1. The figure for the latter, considerably above the average, was based on relatively few deaths. Final returns may not bear out this finding. Among the married women, the mortality ratios for all causes rose steadily from a minimum (84) in Social Class 2 to a maximum (117) in Social Class 5. In Social Class 1 it was a little below the average. The diabetes death rates showed the same trend, except that the rate in Social Class 1 was slightly lower than in Social Class 2. The deaths from diabetes in Social Class 1, the smallest of the five classes, were relatively few in number and the preliminary figures therefore may not be representative.

In the specific occupational groups, the diabetes death rate was lowest among mine workers and highest among clerks. In contrast, the lowest rate among the married women was for those whose husbands were building and dock laborers or clerical workers whereas the wives of mine workers showed the highest mortality.

Among males, the social class pattern of mortality from diabetes according to these provisional figures for 1950 differs appreciably from that based on the data for

TABLE 6

Standardized mortality ratios from all causes and from diabetes by social class and for major occupational groups. Occupied and retired men and married women classified according to occupation of husband. Ages 20-64, England and Wales, 1950

Social class	Mortality ratios				Deaths			
	All causes		Diabetes		All causes		Diabetes	
	Men	Married Women	Men	Married Women	Men	Married Women	Men	Married Women
Total	100	100	100	100	84,644	39,555	334	443
1. Professional	97	96	167	86	2,824	1,300	20	12
2. Intermediate	86	84	97	88	12,689	6,083	56	72
3. Skilled	102	101	97	98	40,838	19,417	155	209
Mine workers	138	142	71	222	2,223	1,124	5	20
Transport workers	104	102	89	130	4,448	2,203	16	30
Clerical workers	114	92	143	83	4,189	1,527	20	15
Others	98	99	94	89	29,978	14,563	114	144
4. Partly skilled	94	104	91	109	13,125	6,560	50	76
Agricultural workers	80	102	85	133	2,462	1,340	11	20
Others	97	105	91	100	10,663	5,220	39	56
5. Unskilled	118	117	108	117	15,168	6,195	53	74
Building and dock laborers	83	97	92	81	2,714	1,337	11	13
Others	130	124	114	127	12,454	4,858	42	61

Source: The Registrar General's Decennial Supplement, England and Wales, 1951, Occupational Mortality—Part 1, London: Her Majesty's Stationery Office, 1954.

TABLE 7

Standardized mortality ratios from diabetes by social class among men and among married women classified according to occupation of husband. Ages 20-64, England and Wales, 1921-1923, 1930-1932 and 1950

Social class	Standardized mortality ratios		
	1921-23	1930-32	1950
Occupied and retired men			
1. Professional	125	122	167
2. Intermediate	145	155	97
3. Skilled	92	95	97
4. Partly skilled	75	82	91
5. Unskilled	66	69	108
Married women			
1. Professional		56	86
2. Intermediate		89	88
3. Skilled		104	98
4. Partly skilled		108	109
5. Unskilled		106	117

Source: Same as table 6.

1921-1923 and 1930-1932 (table 7). In the earlier periods the mortality from the disease in the upper classes was definitely higher than in those in the other social class groupings. The death rate fell continuously from Class 2 to Class 5 and was about a third below the average in the latter. Among the married women, however, for whom previous data are available only for 1930-1932, the pattern then was the same as in 1950, with the diabetes death rate rising to a maximum among those whose husbands were partly skilled or unskilled workers.

The figures from the recent study for ages 65 and over are to some extent influenced by differences in the average age at death in the social class and occupational groupings. Nevertheless, it is interesting to note that particularly as regards married women, the percentages show a rather surprisingly good correlation with the standardized mortality ratios at ages 20-64 (table 8). It is interesting also to note that without exception the percentage of deaths from diabetes was higher in women than in men.

TABLE 8

Percentage of deaths from diabetes
by social class and for major occupational groups among men, and among married women
classified according to occupation of husband.
Ages 65 and over, England and Wales, 1950

Social class	Occupied and retired men Deaths			Married women Deaths		
	All causes	Diabetes	Per cent	All causes	Diabetes	Per cent
Total	154,492	837	0.5	41,385	585	1.4
1. Professional	6,275	44	0.7	1,519	14	0.9
2. Intermediate	28,247	211	0.7	7,619	103	1.4
3. Skilled	70,146	380	0.5	19,533	263	1.3
Mine workers	6,578	19	0.3	1,696	23	1.4
Transport workers	5,182	40	0.8	1,538	15	1.0
Clerical workers	4,499	29	0.6	1,209	12	1.0
Others	53,887	292	0.5	15,090	213	1.4
4. Partly Skilled	26,247	109	0.4	7,110	106	1.5
Agricultural workers	9,398	38	0.4	2,565	31	1.2
Others	16,849	71	0.4	4,545	75	1.7
5. Unskilled	23,577	93	0.4	5,604	99	1.8
Building and dock laborers	4,932	19	0.4	1,234	18	1.5
Others	18,645	74	0.4	4,370	81	1.9

Source: Same as table 6.

ABSTRACTS

Adlersberg, David; Schaefer, Louis E.; and Wang, Chun-I (*Dept. of Med. and Chem., Mt. Sinai Hosp., New York, N. Y.*): ADRENAL CORTEX, LIPID METABOLISM, AND ATHEROSCLEROSIS: EXPERIMENTAL STUDIES IN THE RABBIT. Science *120*:319-20, Aug. 20, 1954.

The authors report that cortisone and hydrocortisone produce significant, although moderate, elevation of the plasma lipid fractions in the rabbit. The combination of cholesterol feeding with daily injections of these hormones produces extreme elevation of all plasma lipid fractions, especially of plasma cholesterol. Nevertheless, atherogenesis and deposition of cholesterol in other tissues, in the latter group, is definitely depressed, possibly because of the diminished tissue permeability produced by these hormones.

Aladjem, Frederick; and Rubin, Leonard (*Donner Lab., Div. of Med. Physics, Univ. of California, Berkeley, Calif.*): SERUM LIPOPROTEIN CHANGES DURING FASTING IN RABBITS. Am. J. Physiol. *178*:267-68, August 1954.

Sixteen rabbits were fasted for 7 days; serum lipoprotein measurements were made during this time. After 3 days of fasting, the concentration of the standard S_f 0-12, 12-20, 20-100 and 100-400 groups of serum lipoproteins all increased significantly. After 7 days of fasting, the level of standard S_f 0-12 serum lipoproteins further increased significantly. The concentration of standard S_f 12-20 and 20-100 lipoproteins remained unchanged from that which was present after 3 days of fasting. The standard S_f 100-400 group of lipoproteins decreased after 7 days of fasting and was again at the prefasting level.

Alpert, Elmer (*First (Columbia) Div. of Bellevue Hosp., New York, N. Y.*): NUTRITION IN DIABETES. New York S. J. Med. 53:2607-10, Nov. 15, 1953.

The author states that the ultimate goal in treating the diabetic patient is the prevention of the vascular degenerative complications. Although its achievement is not immediately at hand, it is suggested that progress in this direction will be made by optimal control of the metabolic abnormality. According to the author, this can be accomplished by insulin therapy when necessary, provision of a diet adequate in calories, and proteins and minerals which may be supplemented by a suitable vitamin formula.

Anderson, George E. (*State Univ. of New York Coll. of Med., New York, N. Y.*): REHABILITATION OF INSULIN FUNCTION IN CLINICAL DIABETES. Postgrad. Med. *16*: 229-37, September 1954.

The author employs a six-minute response to intravenous glucagon-free insulin to measure the patient's intrinsic insulin function and response to therapy. On the basis of this test he divides diabetics into the following three groups: 1. Obese diabetics, poorly controlled, who are not sensitive to the intravenously administered insulin. 2. Juvenile diabetics who, in general, are sensitive to extrinsic insulin regardless of state of control. 3. "Brittle" diabetics whose responses are erratic. Proper dietetic management, particularly in the first group, results in increased sensitivity to injected insulin, which the author feels is a measure of intrinsic insulin production.

Ashe, Benjamin (*Dept. of Med., New York Univ. Postgraduate Med. Sch., New York, N. Y.*): NPH-50 INSULIN: ITS NATURE AND USES. New York S. J. Med. 53:1539-40, July 1, 1953.

A description of NPH insulin is presented in a series of "Current Concepts in Diabetes," published by the Committee on Professional Education of the Clinical Society of the New York Diabetes Association.

Ashe, Benjamin (*Dept. of Med., New York Univ., Bellevue Med. Center, Postgraduate Med. Sch., New York, N. Y.*): THE PRESENT STATUS OF VARIOUS TYPES OF INSULIN AND RECOMMENDATIONS CONCERNING THEIR USE. New York S. J. Med. 53:2761-64, Dec. 1, 1953.

Data are given regarding the nature, time-action, and indications for use of four types of insulin: (1) unmodified insulin (amorphous or crystalline zinc), (2) globin-zinc insulin, (3) NPH insulin and, (4) protamine zinc insulin. (Current Concepts).

Bartlett, Grant R.; and Marlow, Arthur A. (*Scripps Metabolic Clin., La Jolla, Calif.*): COMPARATIVE EFFECTS OF THE DIFFERENT FORMED ELEMENTS ON NORMAL HUMAN BLOOD GLYCOLYSIS. J. Appl. Physiol. *6*:335-47, December 1953.

On the basis of their findings, the authors state that the base level of pure erythrocyte glycolysis is 35 mg. glucose per 100 ml. red cells per hr. when incubated in plasma at normal blood hematocrits in air at 38°C. For reference use, this value was also calculated in terms of moles and molecules/u weight, volume and number of cells. The corresponding Q aerobic glycolysis (lactic) value was 0.228. Normal human blood was found to have a glycolytic rate 5 to 10 per cent higher than its purified red cells. The difference is said to be due to the combined effects of the leucocytes, platelets, and reticulocytes. It was estimated that most of this effect is white cell metabolism.

The WBC/RBC glycolytic activity ratio in normal whole blood was 10 to 20 on a dry-weight basis which gave a white cell Q aerobic lactic value of 2.3 to 4.6. Certain blood fractions in which the white cells had been concentrated by experimental manipulation showed a higher than expected glycolysis. There was no evidence for different metabolic rates at different levels of a centrifugal column of red cells. Specimens of rat and rabbit blood, although differing in absolute metabolic rates, showed approximately the same relative ratios for whole blood to purified cells, as found with human blood.

From a survey of the literature the following estimates of high normal Q aerobic glycolytic values were made: leucocyte-10, platelet-5, and reticulocyte-1. Using these values, the authors calculated the expected contributions of each component to glycolysis in a typical normal blood to be as follows: erythrocytes 80 per cent, leucocytes 15 per cent; platelets 3 per cent; and reticulocytes 2 per cent. The calculated leucocyte/erythrocyte activity ratios were 122/cell, 44/u weight and 20/u volume. Subtracting for the metabolically inert hemoglobin, the WBC/RBC activity was estimated to be 2.6. According to the authors, these values are somewhat higher than found experimentally, due either to the choice of too high Q values or to a lack of correlation between activity and cell concentration in the presence of a large mass of red cells.

Bartlett, Grant R.; Savage, Evelyn; Hughes, Lenore; and Marlow, Arthur A. (*Scripps Metabolic Clin., La Jolla, Calif.*): CARBOHYDRATE INTERMEDIATES AND RELATED COFACTORS IN THE HUMAN ERYTHROCYTE. J. Appl. Physiol. *6*:51-6, July 1953.

An ion-exchange resin technic was used for identification and quantitative analysis of phosphorylated carbohydrate intermediates and adenine derivatives in the human erythrocyte.

Beaser, Samuel B. (*Harvard Med. Sch.; Beth Israel Hosp., Boston, Mass.*): DIABETES MELLITUS. New England J. Med. *251*:698-705, Oct. 21, 1954. *251*:737-43, Oct. 28, 1954.

In a review article on medical progress in diabetes mellitus, the author discusses the following aspects: biochemistry and physiology; pathology and pathogenesis; diagnosis; associated conditions; treatment; pregnancy and diabetes; and complications.

Berens, James J.; Baggenstoss, Archie H.; and Gray, Howard K. (*Sect. of Surg. and Pathologic Anat., Mayo Clin. and Mayo Foundation, Rochester, Minn.*): DUCTAL CHANGES IN CHRONIC PANCREATITIS. A.M.A. Arch. Surg. *68*:723-33, June 1954.

Specimens of pancreas obtained at necropsy in sixteen cases of chronic pancreatitis encountered at the Mayo Clinic were studied with particular reference to the presence or absence of ductal dilatation. The duct of Wirsung was found to be grossly dilated in the tail of the pancreas in seven cases. In four other cases, histologic evidence of dilatation was observed in the smaller ducts and ductules. Factors probably contributing to the dilatation of the ducts were pancreatic lithiasis in two cases, choledocholithiasis in two cases, and foci of necrosis and inflammation in three cases. In the four cases in which histologic evidence of dilatation of small ducts and ductules was present, focal inflammatory foci or ductal metaplasia may have been responsible. The relationship of ductal obstruction to the cause and progression of chronic pancreatitis is discussed in regard to a consideration of surgical retrograde decompression of the pancreatic duct.

Berger, Herbert (*Staten Island, N. Y.*): THE DISAPPEARANCE OF RAYNAUD'S PHENOMENON IN A DIABETIC AFTER THE ADMINISTRATION OF A NEW LIVER

EXTRACT. New York S. J. Med. 53:3030-31, Dec. 15, 1953.

In a case of diabetes with Raynaud's syndrome, the author believed that the use of extract of pregnant mammalian liver was beneficial.

Bing, R. J.; Siegel, A.; Vitale, A.; Balboni, F.; Sparks, E.; Taeschler, M.; Klapper, M.; and Edwards, S. (*Dept. of Med. and Physiol., Med. Coll. of Alabama, Birmingham, Ala.*): METABOLIC STUDIES ON THE HUMAN HEART IN VIVO. I. STUDIES ON CARBOHYDRATE METABOLISM OF THE HUMAN HEART. Am. J. Med. *15*:284-96, September 1953.

The myocardial extraction and usage of glucose, lactate, and pyruvate were measured in 53 patients with and without cardiac failure. The relative contribution of the catabolism of these substances to the oxidative metabolism of the heart (the oxygen extraction ratio) and the conversion of oxidative energy from these carbohydrates into cardiac work (the energy conversion factor) were estimated. It was found that usually the total aerobic metabolism of glucose, lactate, and pyruvate combined, fell short of the total oxygen consumption of the heart. Consequently, the authors deduced that the heart used for provision of energy either heart muscle glycogen or non-carbohydrate substances, the latter possibility appearing more likely.

A spontaneous rise in arterial glucose and lactate concentration was followed by an increase in myocardial extraction and usage. The myocardial extraction of glucose was a function of the logarithm of its arterial concentration while the myocardial lactate extractions plotted against the logarithm of the arterial lactate level followed a parabolic curve. At glucose blood concentrations above 110 mg. per 100 cc. no further uptake of glucose by the myocardium was noticeable. When the arterial blood glucose concentration was suddenly raised, as the result of infusion, an upper limit of glucose extraction appeared to be absent. The authors suggest that this might have resulted from glycogenesis as well as increased oxidation of glucose. Pyruvate was utilized by the human heart.

In low and high output failure, myocardial glucose and lactate extractions and the glucose and lactate extraction ratios were elevated; the glucose and lactate energy conversion factors were lowered. The authors interpret this to indicate that the hyper- and hypokinetic heart in failure has become deficient in converting the energy derived from the aerobic breakdown of glucose and lactate into mechanical work.

Black, Kenneth (*St. Bartholomew's Hosp., London, England*): TUMOURS OF THE PANCREAS: WITH PARTICULAR REFERENCE TO SPONTANEOUS HYPOGLYCAEMIA. Practitioner *173*:264-70, September 1954.

The author reviews the symptoms of carcinoma of the pancreas, and the diagnostic problem presented by spontaneous hypoglycemia.

Blanchaer, Marcel C.; and Baldwin, S. L. (*Dept. of Physiol. and Med. Res., Univ. of Manitoba, Winnipeg, Canada*): PYRUVATE ACCUMULATION IN PRESERVED BLOOD. J. Appl. Physiol. *6*:8-14, July 1953.

A biphasic rise in pyruvate was found in sterile blood kept at 5°C in an acid citrate-dextrose preservative solution. An initial transient pyruvate increase coincided with the rapid disappearance of most of the 2, 3-diphosphoglycerate from the erythrocytes. This was followed by a second, sustained rise in pyruvate, which could be partially inhibited by cyanide and by deoxygenation of the blood. The second pyruvate increase was absent in congenital methemoglobinemic blood. From these findings the authors concluded that a portion of the terminal pyruvate increase in preserved blood was due to a partial aerobic coupling of 3-phosphoglyceraldehyde oxidation through DPN, a flavoprotein and a hemoprotein. As a result, a portion of the pyruvate formed from the products of 3-phosphoglyceraldehyde oxidation was not reduced to lactate and so accumulated.

Bornstein, J. (*Dept. of Biol. Chem., Washington Univ. Sch. of Med., St. Louis, Mo.*): INSULIN-REVERSIBLE INHIBITION OF GLUCOSE UTILIZATION BY SERUM LIPOPROTEIN FRACTIONS. J. Biol. Chem. *205*:513-19, November 1953.

Lipoprotein fractions obtained from serum of diabetic rats by a flotation procedure or by fractionation with alcohol produced, in vitro, an insulin-reversible inhibition of the glucose uptake by diaphragm. The inhibitor was associated with the B_1-lipoprotein fraction and was inactivated by freezing or by standing in an ice bath. The serum of diabetic rats after removal of the lipoproteins by flotation was not inhibitory. Normal rat or human serum and serum from hypophysectomized diabetic rats did not yield an inhibitory lipoprotein fraction. An inhibitory lipoprotein fraction was obtained from the blood of a human subject during hypoglycemia induced by the

injection of a large dose of insulin.

Glutathione synthesis in liver slices from fasted rats, incubated in a medium containing glucose, was inhibited by a lipoprotein fraction obtained from serum reversed by the addition of insulin. The same portion did not inhibit glutathione synthesis in liver slices from fed rats. According to the author this appears to localize the insulin-reversible inhibition at the level of the hexokinase system.

Bornstein, J.; and Park, C. R. (*Dept. of Biol. Chem., Washington Univ. Sch. of Med., St. Louis, Mo.*): INHIBITION OF GLUCOSE UPTAKE BY THE SERUM OF DIABETIC RATS. J. Biol. Chem. *205*:503-11, November 1953.

The authors found that serum from alloxan-diabetic rats inhibited the uptake of glucose in vitro by the diaphragm of normal fasted rats. This inhibitory effect was reversed by insulin in vitro. Serum from diabetic rats which had been adrenalectomized or hypophysectomized did not inhibit glucose uptake. The injection of both growth hormone and cortisone into diabetic hypophysectomized rats restored the inhibitory property of the serum. The injection of either substance alone did not restore inhibition, and the addition to the serum in vitro of the substance not injected was also ineffective. Growth hormone and cortisone added simultaneously to the serum had no effect on glucose uptake. From these findings the authors conclude that the insulin-reversible inhibition of glucose uptake in the blood of diabetic rats is formed as a result of endogenous pituitary and adrenal cortical activity.

Bottoni, A. CONSIDERATIONS ON THE THERAPY OF DIABETIC RETINOPATHY. (Abstr. from Am. J. Ophth. *37*: 624, April 1954: Gior. ital. oftal. *4*:332-34, July-August 1953.

The author discussed the use of methionine and choline, vitamin B, rutin, vitamin P, vitamin E, and testosterone in 115 cases.

Britain, Mary Jane (*Mobile Infirmary Sch. of Nursing, Mobile, Ala.*): AT CAMP WITH DIABETIC CHILDREN. Am. J. Nursing, *54*:1129, September 1954.

The author reviews her experience as a student nurse while working at a diabetic children's camp.

Brun, Claus; Gormsen, Harald; Hilden, Tage; Iversen, Poul; and Raaschou, Flemming (*Med. Dept. III of Kommunehospitalet, and Univ. Inst. of Forensic Med., Copenhagen, Denmark*): DIABETIC NEPHROPATHY. KIDNEY BIOPSY AND RENAL FUNCTION TESTS. Am. J. Med. *15*:187-97, August 1953.

Kidney biopsy findings in 12 cases of diabetes mellitus were compared with the clinical and laboratory findings and the results of several renal function tests. The kidney biopsies were performed by a method developed by Iversen and Brun. In 6 cases the biopsy specimen revealed solely diffuse glomerular changes; in four cases nodular-diffuse changes; and in one case completely hyalinized glomeruli with remnants of nodules; in one case the biopsy showed normal renal tissue in a patient in whom the further course of the disease showed that the renal symptoms must have been due to cardiac failure. The kidney biopsy method made possible correction of chronically misdiagnosed diabetic nephropathy in one case, and in four cases which did not show definite clinical signs of diabetic renal disease it revealed the presence of glomerular changes (diffuse in three cases and nodular-diffuse in one case). The authors contend that biopsy of the kidney, therefore, has some diagnostic value in diabetic nephropathy. Its value in the differential diagnosis of chronic pyelonephritis, on the other hand, is considered to be very limited.

The authors interpret their findings as apparently supporting the theory that diabetic nephropathy originates as diffuse hyalinization in the basement membranes of the glomerular tufts, and that the nodular changes may be considered a further development of the diffuse form. Also, the discrete renal function tests, which alone do not permit any safe diagnostic conclusions with regard to the degree and nature of diabetic nephropathy, are considered to indicate that glomeruli with rather pronounced changes of diabetic origin, at least in some instances, have a higher filtration capacity than might be supposed from the histologic picture.

Byers, Sanford O.; Friedman, Meyer; and Rosenman, Ray H. (*Harold Brunn Inst., Mt. Zion Hosp., San Francisco, Calif.*): HEPATIC SYNTHESIS OF CHOLESTEROL IN NEPHROTIC RATS. Am. J. Physiol. *178*:327-30, August 1954.

The nephrotic state was produced in rats by injection of rabbit antirat-kidney serum. At various stages in the development of progressive hypercholesteremia, the hepatic rate of synthesis of cholesterol was determined by

means of analysis of the biliary cholesterol excretion. The results demonstrated either an unchanged or a diminished hepatic synthesis of cholesterol by the nephrotic rat. It is suggested that the hypercholesteremia of the nephrotic rat is neither initiated nor maintained by an accelerated rate of synthesis of cholesterol by the liver.

Caldwell, Renwick K. (*Veterans' Administration Hosp., Northampton, Mass.*): DIABETES MELLITUS FOLLOWING ACUTE PANCREATIC NECROSIS. REPORT OF A CASE. New England J. Med. *251*:228-30, Aug. 5, 1954.

A case of acute pancreatic necrosis producing diabetes mellitus is presented. Although a severe psychiatric illness prevented a history and accurate evaluation of physical findings, a pancreatic accident was suspected clinically and confirmed by the subsequent course and post-mortem examination a month later. At autopsy a known, and probably unrelated, carcinoma of the prostate was found to have metastasized extensively. Explanations are offered for the adrenocortical hypertrophy noted at autopsy, and the possible etiologic relation of the adrenocortical change and the pancreatic necrosis is mentioned. Acute pancreatitis and pancreatic necrosis should be considered as possible etiologic factors in diabetic acidosis, especially in the presence of abdominal pain.

Cobley, J. F. C. C.; Harrison, K. S.; Blacket, R. B.; and Hewitt, L. E. (*Diabetic Clin., Royal Prince Alfred Hosp., Sydney, Australia*): OUTPATIENT ASSESSMENT OF THE "NOVO" INSULINS. M. J. Australia *2*:499-501, Sept. 25, 1954.

Clinical trial was carried out in an outpatient diabetic clinic where control is dependent on rough urinary tests for sugar. It would appear that some patients whose condition is not controlled satisfactorily by injections of soluble and protamine zinc insulin, or of soluble insulin twice a day, may do better on "Novo" (lente) insulins. On the other hand, some appear to be worse.

Convincing statistical evidence that the new treatment is better than the old is not demonstrable in this study, but some patients have done well, and the use of a single injection has been of undoubted benefit.

Collens, William S. (*Diabetic Clin. and Med. Serv., Maimonides Hosp., Brooklyn, N. Y.*): REGULATED VERSUS FREE DIET IN THE TREATMENT OF DIABETES MELLITUS. J. Clin. Nutrition *2*:195-203, May-June 1954.

The advantages of diet regulation become apparent in the form of clinical well-being, weight control, minimal glycosuria, approach to normal glycemia, and freedom from hypoglycemia. While the long-term benefits in the form of protection against degenerative vascular changes, nephropathy, and retinopathy are not definitively proved, there are some investigators who find this to be the case. The disadvantages of a free, self-selected diet are seen in the complications arising from unrestricted glycosuria, hyperglycemia, hypoglycemia, and haphazard insulin dosage.

Correa, R.; and Rodriguez, R.: VASCULAR COMPLICATIONS IN DIABETES. Rev. invest. clin. 5:273-96, 1953. (Abstr. from J.A.M.A. *155*:386, May 22, 1954).

Of 1,066 cases of diabetes, 406, or 38.08 per cent, showed cardiovascular complications. Of these, 270 showed these changes in various other regions but not in the lower extremities. Vascular alterations were generally observed during the fourth decade and increased with age. The frequency of vascular complications was similar in both sexes. Fewer such complications appeared in those patients who were not obese. Most patients who had vascular complications required less than 10 units of insulin daily and a diet of 150 to 200 gm. of carbohydrate.

Council on Pharmacy and Chemistry (*535 N. Dearborn St., Chicago 10, Ill.*): HYDROCORTISONE. J.A.M.A. *155*: 442-44, May 29, 1954.

Hydrocortisone may be the principle glycogenic steroid secreted by the adrenal cortex, and under conditions of stress may participate in physiological reactions to a greater degree than cortisone. It produces similar and usually reversible metabolic effects, including hyperglycemia, which may require adjustment of insulin dose in patients with diabetes mellitus. Because of its accompanying physiological actions, the drug usually is contraindicated for the long-term treatment of any condition complicated by severe diabetes mellitus.

Dodge, Mark; Mathy, Marion; Robinson, Arthur W.; and Arms, Arnold V. (*Kansas City, Mo.*): AN ERROR IN BLOOD SUGAR DETERMINATIONS. J. Kansas M. Soc. 55: 502-05, September 1954.

The authors believe that the Somogyi method should be adopted for routine blood sugar determinations, since it gives the true glucose value. It is conveniently adaptable to the average office and hospital. The blood sugar determined by Folin-Wu procedure now in common use includes from 10 to 63 mg. of reducing substance which remains after glucose is removed by fermentation.

Periodic fasting blood sugar determinations in diabetics have revealed a variable and inconstant amount of nonglucose reducing substance ranging from 12 to 57 mg. per 100 cc. Also glucose tolerance tests reveal that during a four-hour determination there may be as much as 49 mg. per 100 cc. variation between glucose and total reducing substance in the blood.

Editorial (*160 St. Ronan Street, New Haven, Conn.*): DIABETES DRIVE. Connecticut M. J. *18*:847, October 1954.

The "Diabetes Detection Drive" promoted annually by the American Diabetes Association during Diabetes Week initially placed emphasis on the attempt to find unknown diabetics. In recent years, emphasis has also been placed on the educational phase of the program.

This and other educational factors explain the decrease in admissions of diabetics in coma to the major hospitals.

Fabrykant, Maximilian (*Dept. of Med., New York Univ. Post-Graduate Med. Sch., New York, N. Y.*): ELECTROLYTE DISTURBANCES IN DIABETES. New York S. J. Med. 53:2317-20, Oct. 15, 1953.

The nature and underlying mechanisms of electrolyte disturbances in diabetic acidosis are discussed with emphasis on disturbances in potassium. This article is one of a series dealing with current concepts.

Fabrykant, Maximilian; and Ashe, Benjamin I. (*Dept. of Med., New York Univ. Post-Graduate Med. Sch., and Fourth Med. (NYU) Div., Bellevue Hosp., New York, N. Y.*): PREVENTION OF LOCAL SKIN REACTIONS TO INSULIN. New York S. J. Med. 53:3019-21, Dec. 15, 1953.

The painful skin reactions which commonly develop at the site of insulin injections are considered by the authors to represent nonspecific inflammatory changes which can be prevented by proper injection technic. The technic which proved successful in this regard in over 200 patients is described in detail. The nonpainful tumefactions and fat atrophies are attributed to repeated injury of the injected tissue and are also considered preventable by the use of proper injection technic and frequent varying of the injection sites. With these simple measures, the authors believe it is possible to avoid daily fluctuations in insulin requirement related to local skin reactions and thereby to achieve a better control of diabetes.

Fawcett, Robert M. (*Lake Region Clin., Devils Lake, N. D.*): OBSERVATIONS ON INSULIN REQUIREMENT IN KIMMELSTIEL-WILSON DISEASE. Journal-Lancet 74:327-30, 389, September 1954.

In a case of presumptive Kimmelstiel-Wilson's disease there was transition from an unusually high to a very low-insulin requirement in a relatively short period of time.

Fazekas, Joseph F.; and Bessman, Alice N. (*Georgetown and George Washington Univ. Med. Divs., Gallinger Municipal Hosp., Washington, D. C.*): COMA MECHANISMS. Am. J. Med. *15*:804-12, December 1953.

A physiologic classification of cerebral metabolic disturbances is presented, based on the premise that energy required for functional activity and structural integrity of cerebral cells results from enzymatically catalyzed reactions between glucose and oxygen. Insufficiency of glucose (preferential substrate of the cerebral cells) or oxygen, or inhibition or lack of essential enzymes necessary for the degradation of glucose will result in cerebral metabolic disturbances. The variable response of the central nervous system to the deprivation of these essential substances is believed to be due to their availability and differential rates of utilization by various areas of the central nervous system. The causes of coma are divided into four categories: Substrate insufficiency, enzymatic disturbances, oxygen insufficiency, and multiple etiologies are analyzed along these lines. Clinical examples along with observations of cerebral hemodynamics and metabolism of representative disturbances for each group are presented wherever possible.

Feinberg, H.; Rubin, L.; Hill, R.; Entenman, C.; and Chaikoff, I. L. (*Dept. of Physiol., Sch. of Med. and Donner Lab. of Med. Physics, Univ. of California, Berkeley, Calif.*): REDUCTION OF SERUM LIPIDES AND LIPOPROTEINS BY ETHIONINE FEEDING IN THE DOG. Science *120*:317-18, Aug. 20, 1954.

In addition to the previously reported fatty liver, the authors noted that the feeding of ethionine resulted in a prompt reduction in the levels of serum fatty acids, phospholipides, and cholesterol. At the end of 25 days, negligible amounts of these lipides remained in serum. A reduction in the levels of low- and high-density lipoproteins also resulted from the feeding of ethionine. In general, the extent of reduction in all lipoprotein fractions paralleled that observed in lipides. The removal of ethionine from the diet led to a prompt restoration of the concentrations of all lipid and lipoprotein constituents to normal. It is hypothecated that interference with the formation of lipid-carrying proteins in the liver is responsible for both the development of the fatty liver and a decrease in the serum concentration of all lipides.

Feldman, Noah (*Irvington, N. J.*): OCULAR PALSY AS A COMPLICATION OF DIABETES. J. M. Soc. New Jersey *51*:379-80, September 1954.

The author reports a case of ocular palsy complicating diabetes and reviews the literature.

Flinn, Lewis B.; and Richardson, E. M. (*Metabolic Div., Dept. of Med. and Biochemical Lab., Delaware Hosp., Wilmington, Del.*): A SURVEY OF BLOOD LIPIDS IN SIX DIABETIC PATIENTS. Delaware M. J. *26*:153-59, July 1954.

Six diabetic patients of similar status have been examined for evidence of degenerative vascular disease by the usual clinical means and by a number of laboratory procedures. None of the laboratory tests used was found to be significant in evaluating vascular disease. Regular insulin administered before a fat test meal was followed by markedly increased serum turbidity, three to four hours after the test meal in three of these patients and also in certain other individuals similarly examined, nondiabetic as well as diabetic. In all of the six diabetics and in all of the controls except one, the serum turbidity was increased after insulin when compared with the same individual's serum without insulin.

Foglia, V. G. (*Inst. Biol. and Exper. Med., Buenos Aires, Argentina*): FACTORS WHICH ACCELERATE OR DELAY THE APPARITION OF PANCREATIC DIABETES IN THE RAT. Acta physiol. latinoam. *3*:96-101, 1953.

After removal of 95 per cent of the pancreas in the albino rat, fasting hyperglycemia appears only one to eight months after pancreatectomy. The date of onset of fasting hyperglycemia is easy to determine and marks the end of two normoglycemic stages called prediabetes without special symptomatology, and incipient diabetes with symptoms appearing and increasing in severity. Following the onset of fasting hyperglycemia, a stage of manifest diabetes begins. The onset of manifest diabetes can be delayed by: (1) removing less than 95 percent of the pancreas; (2) diet low in calories or rich in proteins; (3) estrogens, thyroidectomy, and thiouracil. On the contrary, it is accelerated by removing more than 95 per cent of the pancreas; by the use of a diet rich in calories or in certain fats; or by administration of androgens or desiccated thyroid. (Spanish)

Forsgren, Erik (*Länssanatoriet, Svenshögen, Sweden*): LIVER RHYTHM, INSULIN SENSITIVITY AND INSULIN THERAPY. Nord. med. *52*:1334-36, Sept. 23, 1954.

The liver has a rhythmic, pulsating activity. .In the assimilatory phase the weight of the liver increases 2 to 3 times, and the liver assimilates 200 to 300 grams glycogen; its highest point of activity is reached during the night. In the secretory phase, the glycogen disappears through consumption in the liver, assimilation by the blood or transformation into fat; its highest point occurs generally in the middle of the day, and thereafter the liver performs as a sugar consumer. In diabetes, one should give insulin in the morning so as to control the hepatogenic sugar wave and in the afternoon to control the postalimentary sugar wave and counteract the tendency toward acidosis. In the middle of the day, excessive insulin stimulants should be avoided, provided one will not for psychotherapeutic purposes induce a hypoglycemic coma. Only in mild cases of diabetes is a morning dose of insulin sufficient. When the daily requirement exceeds 30 or 40 units, two insulin doses should be given. In fatty or amyloid degeneration of the liver, one must resort to slower-acting insulin and replace the hepatogenic sugar wave in the morning with an extra supply of nourishment. Insufficient and unrhythmic insulin

treatment causes undernourishment, which can make one susceptible to tuberculosis. (Swedish)

Frantz, Ivan D., Jr.; Schneider, Henny S.; and Hinkelman, Beverly T. (*Cardiovascular Res. Lab., Dept. of Med., Mass. Gen. Hosp. and Harvard Med. Sch., Boston, Mass.*): SUPPRESSION OF HEPATIC CHOLESTEROL SYNTHESIS IN THE RAT BY CHOLESTEROL FEEDING. J. Biol. Chem. *206*:465-69, January 1954.

Rats fed a diet to which had been added 1 per cent of cholesterol showed a large rise in the concentration of liver cholesterol but only a minimal rise in the serum cholesterol. The serum cholesterol of rats with damaged thyroid glands was slightly higher than that of the controls, even on a normal diet. After cholesterol feeding, the rise was greater than in animals with normal thyroid glands. The liver cholesterol rose at least as much after cholesterol feeding as in rats with normal thyroids. The action of the liver could be viewed, according to the authors, as that of a buffer for the serum cholesterol. The rate of hepatic cholesterol synthesis appeared to depend on the liver's cholesterol content and to be very sensitive to it.

There was no evidence that inhibition of cholesterol synthesis by dietary cholesterol is mediated through the thyroid gland; synthesis was inhibited to at least as great an extent in animals which had received radioactive iodine as in normal rats.

Futcher, P. H.; and Long, N. W., Jr. (*Dept. of Med. and Obstet., Johns Hopkins Univ. Sch. of Med. and Hosp., Baltimore, Md.*): HOSPITAL DATA ON THE BIRTH OF LARGE INFANTS TO "PREDIABETIC" WOMEN. Bull. Johns Hopkins Hosp. *94*:128-38, March 1954.

Data from hospital records have been presented on 98 pregnancies in 46 "prediabetic" mothers who were first recognized as manifesting diabetes mellitus two or more years after the pregnancy. The mean weight of the 98 infants was significantly greater than that of a control group of infants. Prolongation of the period of gestation was not a requirement for the development of a heavy infant. Obesity and relatively high parity were frequent, but not constant, characteristics of the mothers of heavy infants.

Gais, Elmer S. (*Montefiore Hosp., New York Univ. Postgraduate Sch., and Fourth (NYU) Med. Div., Bellevue Hosp., New York, N. Y.*): DIABETES AND TUBERCULOSIS. New York S. J. Med. *53*:1844-46, Aug. 15, 1953.

The incidence and management of diabetes complicated by tuberculosis is discussed with emphasis on early detection and prompt vigorous treatment of both diseases.

Gerritzen, F. (*Laan van Koot 37, The Hague, Netherlands*): THE DURATION OF ACTION OF A ZINC-INSULIN-PROTAMINATE. München. med. Wchnschr. *96*:493-94, April 23, 1954.

Various insulin preparations of Hormon-Chemie were examined by means of a method in which the insulin effect was followed on healthy students with a constant carbohydrate supply. Regular insulin "Horm" corresponds in its action to crystalline insulin, while the action of depot insulin "Horm" has a striking similarity to that of NPH. (German)

Gill, D. G. (*Dept. of Health, Montgomery, Ala.*): BANTING, INSULIN AND DIABETES. J.M.A. Alabama *24*: 75-77, September 1954.

The author presents a biographical eulogy of Banting and his discovery of insulin.

Grant, Joseph L. (*Veterans Administration Hosp., White River Junction, Vt.; Mary Hitchcock Memorial Hosp., Hanover, N. H.; Dartmouth Med. Sch., N. H.*): ELEVATED GLUCOSE THRESHOLD IN KIMMELSTIEL-WILSON SYNDROME. New England J. Med. *251*:302-04, Aug. 19, 1954.

A group of 10 patients with Kimmelstiel-Wilson syndrome is described. These patients averaged sixty years of age at death, and had had diabetes for approximately twice as long as a comparable series of diabetic patients without intercapillary glomerulosclerosis. The clinical course in two cases is described, and it is stated that a characteristic feature of the group appears to be an increase in the renal threshold for glucose. This is believed to result from a decrease in renal plasma flow and glomerular filtration rate. It may result in un-

recognized hyperglycemia if patients are followed only by tests for glycosuria.

Greenhouse, Barnett (*Grace-New Haven Community Hosp., New Haven, Conn.*): LENTE INSULIN. Connecticut M. J. *18*:848-49, October 1954.

The author describes his experience with lente insulin, and compares it with other preparations having an intermediate action—NPH and globin insulin. Subtle differences in action may be observed between the three insulins, giving the physician a wider choice of insulin effects. However, lente insulin has a longer action approaching that of protamine zinc insulin. He finds that generous bedtime feedings are necessary to prevent insulin reactions during the night, and that an added dose of regular or crystalline insulin is often needed to hasten the insulin effect at breakfast.

The advantages of lente insulin in its present form lie not in clinical superiority to the NPH or globin insulin, but rather in the elimination of foreign protein modifying agents.

Günther, Otfried (*Diabetikerheim Garz und Karlsburg, Germany*): LOCAL INSULIN FAT ATROPHY AND ITS PREVENTION. Klin. Wchnschr. *30*:1080-81, Dec. 1, 1952.

At present, insulin fat atrophy can best be prevented by frequent changing of the injection sites. However, this method does not offer a sure guarantee, because local fat atrophy can be observed in the area involved even after a single insulin injection. Developed fat atrophy areas can be made to recede within several weeks by regular injections in the deepest places of the grooves after the method of Collens and associates. This was shown by the author's results in numerous cases. It is necessary also, thereafter, to perform an occasional injection at the site of the removed fat atrophy to prevent relapses. (German)

Hallum, Alton V. (*Dept. of Ophthal., Emory Univ. Sch. of Med., and Grady Clay Memorial Eye Clin., Grady Hosp., Atlanta, Ga.*): THE OCULAR MANIFESTATIONS OF DIABETES. South. M. J. *47*:590-94, June 1954.

The literature concerning the manifestations of diabetes in the various parts of the eye is reviewed, including evidence that endocrine hyperactivity is a factor in producing retinopathy.

Hansen, R. G.; Craine, E. M.; and Gray, P. (*Lab. of Biochem., Dept. of Dairy Science, Univ. of Illinois, Urbana, Ill.*): LACTOSE METABOLISM. III. THE REVERSIBLE CONVERSION OF GALACTOSE-1-PHOSPHATE TO GLUCOSE-1-PHOSPHATE. J. Biol. Chem. *208*:293-98, May 1954.

The reversibility of the galactose-1-phosphate glucose-1-phosphate transformation was demonstrated by (1) the detection of the carbon-labeled galactose ester after incubation of carbon-labeled glucose-6-phosphate with bacterial extracts, and (2) the detection of galactose formation from glucose-1-phosphate after purification of bacterial extracts to eliminate phosphoglucomutase. The equilibrium of this reaction was estimated at about 21 to 27 per cent of the galactose ester and 73 to 79 per cent of the glucose ester.

Hardgrove, Maurice (*Marquette Univ. Sch. of Med., Milwaukee, Wis.*): DIABETES MELLITUS. Postgrad. Med. *16*:28-33, July 1954.

Diabetic problems vary in different age groups. The essentials of clinical and chemical control should be emphasized in both the treatment of acidosis and the long-term management of the diabetic. The discovery of a person with diabetes stimulates the physician to search for additional diabetics in the patient's family and relatives.

Haugaard, Ella S.; and Haugaard, Niels (*John Herr Musser Dept. of Res. Med., Univ. of Pennsylvania, Philadelphia, Pa.*): THE EFFECT OF HYPERGLYCEMIC-GLYCOGENOLYTIC FACTOR ON FAT METABOLISM OF LIVER. J. Biol. Chem. *206*:641-45, February 1954.

Further observations are reported on the action of the hyperglycemic-glycogenolytic factor on the metabolism of fat by rat liver slices. The authors found that, in addition to acetate, the utilization of radioactive glucose and fructose for fatty acid synthesis was inhibited by this substance. It was also shown that hyperglycemic-glyco-

genolytic factor increased the formation of ketone bodies by rat liver slices, both in the absence of substrate and in the presence of acetate.

Haugaard, Niels; Vaughan, Martha; Haugaard, Ella S.; and Stadie, William C. (*John Herr Musser Dept. of Res. Med., Univ. of Pennsylvania, Philadelphia, Pa.*): STUDIES OF RADIOACTIVE INJECTED LABELED INSULIN. J. Biol. Chem. *208*:549-63, June 1954.

Radioactive sulfated or iodinated insulin was administered to dogs and rats, and the distribution of radioactive material in the tissues and its excretion in the urine were determined. Evidence was obtained that no appreciable removal of sulfate or iodide from the labeled insulin molecule took place in the animal and that the radioactivity determined corresponded to unchanged labeled and insulin inactivation products of insulin formed in the body. A rapid excretion of radioactive substances in the urine of dogs and rats was noted after administration of sulfated or iodinated radioactive insulin. These substances, in contrast to the original radioactive labeled insulin, were quite readily dialyzable, which indicated that the labeled insulin molecules had undergone degradation in the body.

The concentration of radioisotope was found to vary widely from tissue to tissue after administration of isotopic insulin, with a distribution different from that obtained after injection of radioactive iodinated albumin or free sulphate. The authors interpreted these findings as reflecting the ability of the various tissues to concentrate the injected insulin preparations. Liver and kidney appeared to have the greatest ability to concentrate injected insulin, while little or no insulin entered the brain.

Hausberger, F. X.; Milstein, Seymour W.; and Rutman, Robert J. (*Depts. of Anat. and Biochem., Jefferson Med. Coll., Philadelphia, Pa.*): THE INFLUENCE OF INSULIN ON GLUCOSE UTILIZATION IN ADIPOSE AND HEPATIC TISSUES IN VITRO. J. Biol. Chem. *208*:431-38, May 1954.

In an attempt to compare the relative abilities of liver and adipose tissue to form fat, the authors measured the ratio of conversion of radioactive glucose to fatty acid and carbon dioxide in vitro by both tissue of rats fed Purina chow. In addition, the effects of untreated alloxan-induced diabetes and insulin-controlled diabetes on the fat-forming and oxidative capacities of liver and adipose tissue were studied. According to the authors, if the large difference between the lipid and protein content of the two tissues is taken into account, adipose tissue appeared to be far more active in both capacities than liver. These metabolic features showed the same qualitative tendencies in both tissues when exposed to alloxan diabetes and insulin therapy. Lack or excess of insulin had a more marked effect upon lipogenesis than upon glucose oxidation.

Hayes, Daniel W. (*Sect. of Internal Med., Mahorner Clin.; Louisiana State Univ. Sch. of Med., New Orleans, La.*): INSULIN PREPARATIONS IN THE TREATMENT OF DIABETES MELLITUS. J. Louisiana State M. S. *106*:387-91, October 1954.

For patients with mild diabetes which cannot be controlled by diet alone, the author gives 10 to 40 units of protamine zinc, NPH or globin insulin once daily before breakfast; with moderately severe diabetes in which more than 30 or 40 units of insulin are needed, he uses NPH or globin insulin once daily before breakfast. With severe diabetes he secures good control with NPH or globin once daily in many cases, although in some he achieves better control with a mixture of 2½ or 3 parts of regular insulin to 1 part of protamine zinc insulin. In cases of labile diabetics, there is often need for two injections of NPH or globin insulin each day, usually two-thirds of the total dose in the morning, and one-third twelve hours later. Lente type insulins are described briefly.

Hines, Laurence E.; Catlin, James; and Kessler, Donald L. (*Dept. of Med., Northwestern Univ., Chicago, Ill.*): TESTS FOR SO-CALLED CAPILLARY FRAGILITY OF THE SKIN AND THE SIGNIFICANCE OF POSITIVE TESTS IN VASCULAR DISEASE. Am. J. Med. *15*:175-79, August 1953.

According to the authors, positive capillary fragility or positive tourniquet tests are terms used loosely to describe intracutaneous hemorrhage produced by standardized doses of trauma (suction or venous compression). These tests for capillary fragility are crude and cannot be performed accurately by counting petechiae. Sources of error are said to be numerous and can be overcome only by making numerous tests on different days. In the authors'

studies intracutaneous hemorrhage in the test was graded one to four plus. Inconstant and inconclusive results were discarded.

A higher incidence of positive tests was found in older patients. Patients with diabetes mellitus which coexisted with hypertension or other vascular disease showed an extremely high incidence of positive capillary fragility tests, and this is said to correspond to the well-known high incidence of spontaneous retinal and skin hemorrhages in such patients. Patients with hypertension and also those with arteriosclerotic disease without hypertension showed moderately high incidence of positive fragility tests.

Hinkle, Lawrence E. (*Dept. of Med., Cornell Univ. Med. Sch., Ithaca, N. Y.*): THE DOCTOR-PATIENT RELATIONSHIP IN THE MANAGEMENT OF DIABETIC PATIENTS AND THEIR EMOTIONAL PROBLEMS. New York S. J. Med. 53:1943-45, Sept. 1, 1953.

The discussion is based on the premise that no physician can adequately understand the course of his diabetic patient or effectively help him to manage his disease, unless he knows a good deal about the patient's life history and present life situation. Some of the more commonly encountered attitudes and characteristics of behavior in diabetics are enumerated together with rationale for handling them.

Hotta, S.; Hill, R.; and Chaikoff, I. L. (*Dept. of Physiol., Univ. of California Sch. of Med., Berkeley, Calif.*): MECHANISM OF INCREASED HEPATIC CHOLESTEROGENESIS IN DIABETES: ITS RELATION TO CARBOHYDRATE UTILIZATION. J. Biol. Chem. *206*:835-44, February 1954.

The rates of incorporation of the C^{14} of acetate—1-C^{14} into cholesterol by livers of two groups of alloxan-diabetic rats were compared. One group was fed a diet containing 60 per cent glucose; the other, a diet containing 60 per cent fructose. The capacity of the liver of the glucose-fed, *diabetic* rat to incorporate the C^{14} into cholesterol was more than twice that observed with livers of *normal* rats fed either the high-glucose or the high-fructose diet. The rate of hepatic cholesterogenesis in diabetic rats was restored to normal by the feeding of the high-fructose diet. The authors suggest, on the basis of the evidence presented, that it is reasonable to infer that restoration of glycolytic activity in the diabetic liver induced by fructose feeding is responsible for diverting the C_2 fragment from the path of cholesterol synthesis to other metabolic pathways, presumably lipogenesis.

Howells, Leonard H.: OCULAR COMPLICATIONS OF DIABETES MELLITUS. Brit. J. Ophth. 37:716-24, December 1953.

Retinopathy occurs even in mild and well-controlled diabetes. Diabetic retinopathy is independent of and distinguishable from the effects of arteriosclerosis and hypertension. In the later stages retinal changes characterized by hypertension may be superimposed on those due to diabetes, and in advanced cases it may be impossible correctly to apportion the blame. Retinitis proliferans is known to occur as a late complication of diabetic retinopathy in long-standing cases, the retinal changes being accompanied by hypertension and severe damage to the kidneys.

The fundus picture in diabetes is progressive, and the prognosis is bad. Temporary changes in accommodation, causing either myopia or hypermetropia, may result from changing refraction due to varying sugar content, particularly in patients receiving insulin. Retrobulbar neuritis and diplopia occurs occasionally, and, more rarely, lipemia retinalis, optic tract lesions, optic atrophy, and paralysis of the ocular muscles may be encountered.

Jacobi, Harry G. (*111 East 80th St., New York 21, N. Y.*): NUTRITIONAL STUDIES OF JUVENILE DIABETICS ATTENDING SUMMER CAMP. J. Clin. Nutrition 2:22-31, January-February 1954.

Comparative studies are presented with respect to weight, height, and relationship of weight to height for 155 diabetic children attending Camp NYDA, during the summer of 1951. Similar studies of caloric intake are included. In the boys' group, there was a slight tendency to overheight and underweight. In the girls' group, there was the same tendency to slight overheight but a rather definite and considerable tendency to overweight. Almost two-thirds of our girls' group were overweight. At the end of their camp stay, 40 per cent of the boys showed a gain in weight as compared to 46 per cent who lost

weight. Essentially, the same proportions held true for the girls. Approximately 43 per cent of the boys' group and 25 per cent of the girls' group required an increase in their food allowance during their camp stay; only 2 of the boys and 4 of the girls had their food intake reduced. In addition to the 30 per cent reduction of insulin dosage at time of admission to camp, 17.5 per cent of the boys required further reduction in their insulin dosage as compared to only 13.5 per cent of the girls. On the other hand, about 37 per cent of both boys and girls required an increase in their total insulin dosage above their original home insulin dose, in order to be maintained under good diabetic control. Half of the children entering Camp NYDA had been maintained on NPH insulin alone. Experience with various insulin mixtures is described.

Kantrow, Abraham H. (*Dept. of Pediat., State Univ. Coll. of Med. at New York City, and Dept. of Pediat., Long Island Coll. Hosp. and Kings County Hosp., and Children's Diabetic Clin., Kings County Hosp., State Univ. Div., N. Y.*): MANAGEMENT OF THE DIABETIC CHILD. New York S. J. Med. 53:1741-44, Aug. 1, 1953.

The author states that clinical control of the diabetic state, normal growth (and maturation), and wholesome emotional development are the main goals in managing the diabetic child. The management of the diabetic child is discussed from the standpoint of: diet, insulin, urine testing and diabetic diary, control of infection, diabetic emergencies (coma and insulin shock), medical checkup, and intelligence and emotional stability of the child and his family.

Kuntze, J. (*Medizinische Klinik des Allgemeinen Krankenhauses, Hamburg, Germany*): SIGNIFICANCE OF DAILY BLOOD SUGAR CURVES FOR DIAGNOSIS OF THE DIABETIC METABOLISM CONDITION. Deutsche med. Wchnschr. 79:1048-50, June 25, 1954.

For diagnosis of mild and moderately severe diabetes, the fasting blood sugar determination together with the amount of sugar excreted in the urine are usually sufficient. In the ambulant care of many cases of diabetes, it is possible to be guided by the glycosuria alone, provided that the kidneys are intact. Observation of the blood sugar curves daily may be useful in cases of severe diabetes with labile metabolism, in the presence of complications, in new cases of the disease and in new adjustments and in the testing of new insulins or insulin combinations. (German)

Lamar, Carlos P. (*Dept. of Endocrinol. and Diabetic Clin., Jackson Memorial Hosp., Miami, Fla.*): A NEW WAY OF LIVING FOR DIABETICS. Bull. Jackson Memorial Hosp. & Sch. of Med., Univ. of Miami 8:28-34, July 1954.

The author claims advantages for "a revolutionary new method" of treatment of diabetes with a diet very high in sugar, especially in fructose, based on an experience of fifteen months.

Lawton, Stanley E.; and Mossey, Richard O. (*Depts. of Surg., Presbyterian Hosp., and Univ. of Illinois Sch. of Med., Chicago, Ill.*): PANCREATIC CYSTS. A.M.A. Arch. Surg. 68:734-43, June 1954.

Many factors must be critically evaluated in the selection of an operative procedure for treatment of pancreatic cyst. These include the etiology, anatomy, and pathology involved as well as the general condition of the patient. In addition to total excision of the cyst, which if feasible, is the operation of choice, the surgeon may consider external drainage especially in the treatment of thin-walled cysts or internal drainage by an anastamosis of the cyst with the gastrointestinal tract.

Levin, Marvin E. (*Dept. of Med., Washington Univ. Sch. of Med., St. Louis, Mo.*): SPONTANEOUS REMISSION OF DIABETES MELLITUS: "THE HOUSSAY PHENOMENA IN MAN." Ann. Int. Med. 40:1230-34, June 1954.

A case is reported of spontaneous remission in diabetes mellitus due to the development of hypopituitarism following a cerebral vascular accident. Comment is made on the various diagnostic tests and presumptive location of the lesion.

Lewis, Lena A.; Quaife, Mary L.; and Page, Irvine H. (*Res. Div. of the Cleveland Clin. Foundation, and The Frank E. Bunts Educational Inst., Cleveland, Ohio, and the Lab. of Distillation Products Industries, Div. of Eastman Kodak Co., Rochester, N. Y.*): LIPOPROTEINS OF

SERUM, CARRIERS OF TOCOPHEROL. Am. J. Physiol. *178*:221-22, August 1954.

The authors report that the concentration of serum tocopherol of 14 adult human beings on a usual diet ranged from 0.68 to 2.75 mg. per 100 ml. Tocopherol was concentrated in all lipoprotein fractions but chiefly in the B_2-fraction. Following ingestion of 400 mg. of alpha-tocopherol daily for 3 days, the serum concentrations of tocopherol increased to a greater degree than the increase in the lipoprotein fraction, with 20 per cent not in the lipoprotein concentrate on an ordinary diet and 40 per cent not in this fraction on the high tocopherol intake.

Ling, Chiun T.; and Chow, Bacon F. (*Dept. of Biochem., Sch. of Hygiene and Public Health, Johns Hopkins Univ., Baltimore, Md.*): THE INFLUENCE OF VITAMIN B_{12} ON CARBOHYDRATE AND LIPIDE METABOLISM. J. Biol. Chem. *206*:797-805, February 1954.

The effect of vitamin B_{12} on carbohydrate and lipid metabolism was studied by blood sugar determinations, by glucose tolerance tests, and by estimation of the phospholipid content of blood and tissues. Its possible relationship to the changes in blood glutathione content was also investigated.

Experimental results indicated to the authors that vitamin B_{12} deficiency entails a derangement in carbohydrate utilization and decreases the phospholipid content of blood and tissues. Administration of glutathione or vitamin B_{12} lowered the blood sugar level of rats with hyperglycemia induced by a high carbohydrate-low-fat diet and by glucose injections.

The authors conclude that vitamin B_{12} plays an important role in carbohydrate and lipid metabolism and that the effect of this vitamin on blood glutathione concentration may be of significance in its role in metabolism.

Lowenberg, Robert I. (*Surg. Serv., Grace-New Haven Community Hosp., New Haven, Conn.*): EARLY DIAGNOSIS OF PHLEBOTHROMBOSIS WITH AID OF A NEW CLINICAL TEST. J.A.M.A. *155*:1566-70, Aug. 28, 1954.

The only equipment necessary is a sphygmomanometer in patients suspected of having phlebothrombosis. The pneumatic cuff is placed about the calf or thigh and slowly distended; distention of the cuff should be accomplished in 10 to 15 seconds. Normally, patients do not register discomfort below 180 mm. Hg over the calf or thigh. In the presence of phlebitis, the patient will complain bitterly of pain at a level significantly below the normal.

Marshall, N. B.; and Mayer, J. (*Dept. of Nutrition, Harvard Sch. of Public Health and Dept. of Physiol., Harvard Med. Sch., Boston, Mass.*): ENERGY BALANCE IN GOLDTHIOGLUCOSE OBESITY. Am. J. Physiol. *178*: 271-74, August 1954.

Obesity can be induced when doses approximating the LD_{50} of goldthioglucose dissolved in water (instead of suspended in oil) are administered to mice. Goldthiomalate and sodium thioglucose injected in comparable amounts were not effective. The food intake of goldthioglucose obese mice is 75 to 100 per cent greater than that of nonobese animals; the oxygen consumption is greater than that of the nonobese; and the spontaneous physical activity of goldthioglucose mice is similar to that of nonobese animals. These findings contrast with results obtained from genetically obese mice, which are characterized by slight relative hyperphagia, low-oxygen consumption, and depressed physical activity. This comparison emphasizes the multiple etiology of obesity. Differences in mechanism between obesities of different types are also illustrated by the fact that like hypothalamic hyperphagic rats, but unlike genetically obese mice, goldthioglucose obese mice increase their weight at the greatest rate on high fat diets, at a slower rate on high carbohydrate diets, while they lose weight on high protein diets.

Martin, M. Mencer; and Pond, M. H. (*Depts. of Diabetes and Chemical Pathology, King's Coll. Hosp., London, S.E. 5, England*): PITUITARY INSUFFICIENCY ASSOCIATED WITH DIABETES MELLITUS. J. Clin. Endocrinol. and Met. *14*:1046-55, September 1954.

A case is reported of diabetes mellitus and partial pituitary insufficiency, presenting as myxedema. Thyroid function before and after the administration of thyrotropic hormone (TSH) was tested with radioactive iodine (I^{131}), and on both occasions the thyroidal I^{131} uptake was negligible and suggestive of that observed in myxedema. There was, however, some metabolic response to

TSH. Studies of the total 17-ketosteroid excretion before, during, and after TSH, corticotropin and cortisone administration were carried out. The application of new methods to these investigations has been reported. Corticosteroid excretion was within normal limits, though 17-ketosteroid excretion was minimal. The response of the latter to corticotropin (in which three quarters of the 17-ketosteroid was of adrenocortical origin) suggested some previous abnormal function of the adrenal cortex, in spite of normal corticosteroid excretion. The response to corticotropin and the extreme sensitivity to insulin supported the diagnosis of pituitary insufficiency. The findings are discussed in relation to similar cases in the literature.

Miller, John H. (*Section on Gerontology, Nat. Insts. of Health, P.H.S., D.H.E. and W., Bethesda, and the Baltimore City Hosps., Baltimore, Md.*): EFFECT OF INSULIN ON MAXIMAL RATE OF RENAL TUBULAR UPTAKE OF GLUCOSE IN NON-DIABETIC HUMANS. Proc. Soc. Exper. Biol. & Med. *82*:322-24, November 1953.

The maximal rate of renal tubular reabsorption of glucose (Tm^{G}) was determined before and after the administration of 20 units of crystalline zinc insulin in a series of 12 nondiabetic male subjects aged 47 to 68 years who were free of evidence of cardiovascular or renal disease. Following the administration of insulin, there occurred a slight, but statistically significant, decrease in Tm^{G} during the period extending from 12 to 48 minutes after injection.

Miller, Zelma (*Children's Cancer Res. Foundation, Children's Med. Center, and the Dept. of Pathol., Harvard Med. Sch., Boston, Mass.*): EFFECTS OF AN ADRENOCORTICAL EXTRACT ON TISSUE GLYCOLYSIS IN VITRO. J. Biol. Chem. *208*:327-35, May 1954.

The author observed that Lipo-Adrenal Cortex in vitro increased the aerobic glycolysis of thymus lymphocytes and of slices of brain, kidney, liver, and other tissues at concentrations which had no influence on respiration. The effects observed could not be attributed to cortisone, hydrocortisone, or desoxycorticosterone, and the activity was not affected by insulin. An intact cell was required for this effect. The glycolysis of brain and thymus homogenates was not stimulated. Glycolysis by an extract of rat brain acetone powder was slightly inhibited. Hexokinase, ATPase, and DPNase in cell-free preparations were affected little, if at all. Fructose diphosphate was glycolyzed more rapidly than glucose by intact thymus lymphocytes. This glycolysis was not stimulated by Lipo-Adrenal Cortex. Glycolysis of thymus lymphocytes was also increased in a high osmolar environment.

Mufson, Isidor (*New York*): PERIPHERAL VASCULAR DISEASES AND THEIR CURE. J.A.M.A. *155*:1559-62, Aug. 28, 1954.

The author demonstrates the response made by patients with peripheral arterial obliterative diseases after repeated arterial infusions of histamine to support his thesis that the true objective of treatment is not to release vasospasm but to give impetus to a structural dilation of collateral vessels. He considers histamine is the most effective agent to bring about this change, because it can cause the greatest vasodilatation and increase of blood flow in collateral vessels. He believes that histamine when combined with antibiotics in the arterial infusion offers the best means of treatment of infections complicating peripheral vascular disease.

Nemeth, Andrew M. (*Dept. of Anat., Sch. of Med., Univ. of Pennsylvania, Philadelphia, Pa.*): GLUCOSE-6-PHOSPHATASE IN THE LIVER OF THE FETAL GUINEA PIG. J. Biol. Chem. *208*:773-76, June 1954.

No glucose-6-phosphatase activity in the liver of the fetal guinea pig could be demonstrated until or just before term. According to the author, in view of the absence of this enzyme, the stability of fetal liver glycogen and its great accumulation during the latter part of gestation may be understood.

Nemeth, Andrew M.; Insull, William, Jr.; and Flexner, Louis B. (*Dept. of Embryology, Carnegie Inst. of Washington, Baltimore, Md., and Dept. of Anat., Sch. of Med., Univ. of Pennsylvania, Philadelphia, Pa.*): GLYCOGENESIS IN THE LIVER OF THE FETAL GUINEA PIG. J. Biol. Chem. *208*:765-72, June 1954.

Glycogen was not chemically demonstrable in the liver of the fetal guinea pig up to the 57th day of gestation (term 66 days), although it was present in cardiac and skeletal

muscle at least as early as the 39th day. Phosphoglucomutase, glucose-1, 6-diphosphate, and phosphorylase were demonstrated in the fetal liver before the 57th day of gestation in the same relative quantities as in the adult. Evidence was obtained for the presence of hexokinase and, in homogenates, for the appearance of phosphorylase primer. The authors suggest that the absence of glycogen before the 57th day in the intact hepatic cell is due to an inadequate number of priming end-groups which may reflect a relative deficiency of branching enzyme activity.

Neubauer, Richard A.; Magee, Joseph; Dunsmore, Lillian; and Garrigues, Elizabeth (*Memorial Hosp., Wilmington, Del., Philadelphia Gen. Hosp., Philadelphia, Pa.*): CERTAIN OBSERVATIONS ON SODIUM EXCRETION IN ADVANCED RENAL DISEASE. Am. J. M. Sc. 228:306-11, September 1954.

Urinary sodium excretion was studied in 19 cases of advanced renal disease, 9 of chronic glomerulonephritis, 4 of polycystic kidney and 6 of chronic pyelonephritis, all in uremia and acidosis, and treated with a diet containing 20 to 40 gm. of protein and 12.5 to 20 mEq. of sodium supplemented with 120 to 160 mEq. of 1 or 1½ molar sodium lactate. Regardless of the type of kidney disease, upon institution of hypertonic sodium lactate therapy, a rapid increase in the concentration of sodium in the urine was noted and there was no clinical evidence of edema formation, pulmonary edema or aggravation of an existing hypertension.

Osserman, Kermit E. (*Med. Dept. and Diabetic Clin. of Mt. Sinai Hosp., New York, N. Y.*): COMMON ERRORS BY PATIENTS IN THE MANAGEMENT OF DIABETES. New York S. J. Med. 53:1637-39, July 15, 1953.

Common mistakes made by patients in the management of diabetes are discussed under five headings: (1) errors in administration of insulin, (2) errors in diet, (3) errors in hygiene, (4) errors caused by psychic trauma of diabetes, and (5) errors associated with acute illness. Definite rules are outlined to avoid such errors.

Paalman, Russell J. (*Dept. of Obstet. and Gynec., Butterworth Hosp., Grand Rapids, Mich.*): MANAGEMENT OF DIABETES IN PREGNANCY. Obst. & Gynec. 4:302-07, September 1954.

The author presents a review of the problems concerned with diabetes as a complication of pregnancy.

Petrova, A. N. (*Lab. of Physiol. Chem., Academy of Sciences, USSR, Moscow*): STUDY OF THE PROCESSES OF ENZYMATIC GLYCOGEN DECOMPOSITION IN MUSCLES OF RABBITS WITH ALLOXAN DIABETES. Biokhimiia 17: 469-75, 1952.

During alloxan diabetes undialyzed extract of muscle possesses a considerably reduced capacity to activate the processes of phosphorolytic and of hydrolytic glycogen decomposition in experiments in vitro as compared with extracts of muscle of normal animals. (Russian)

Pilgeram, Laurence O., and Greenberg, David M. (*Dept. of Physiol. Chem., Sch. of Med., Univ. of California, Berkeley, Calif.*): SUSCEPTIBILITY TO EXPERIMENTAL ATHEROSCLEROSIS AND THE METHYLATION OF ETHANOLAMINE-1, 2-C^{14} TO PHOSPHATIDYL CHOLINE. Science 120:760-61, November 1954.

In support of the hypothesis that atherosclerosis is related to phospholipid metabolism as indicated by elevated ratio of cholesterol to phospholipid in human coronary artery disease and by poor clearing of alimentary lipemia in atherosclerotic males which is enhanced by enzyme removal of lecithin (phosphatidyl choline), the authors report a striking difference between the rate of lecithin synthesis from ethanolamine in liver slices from the rat which is immune to gross atherosclerosis and from the guinea pig and chick which are susceptible. Methods which distinguish among the phospholipids suggest that certain but not all phospholipids are necessary for normal cholesterol breakdown or metabolism.

Reid, L. Corsan (*Dept. of Surg., New York Univ. Postgraduate Med. Sch. and Inst. of Physical Med. and Rehabilitation, New York Univ., New York, N. Y.*): THE METABOLIC PATHWAYS OF GLUCOSE. New York S. J. Med. 53:2068-72, Sept. 15, 1953.

Nine principal metabolic pathways of glucose are discussed. A novel analogy has been made between the

pathway traveled by glucose in going to glycogen and in going to carbon dioxide and water over the Krebs cycle and some well-known steps commonly practiced by the lumber industry.

Rifkin, Harold (*Med. Div., Montefiore Hosp., New York, N. Y.*): THE KIMMELSTIEL-WILSON SYNDROME AND ITS VARIANTS. New York S. J. Med. 53:2947-50, Dec. 15, 1953.

Six different clinical variants of the full-blown Kimmelstiel-Wilson syndrome encountered a large group of patients at Montefiore Hospital in New York City are outlined. The relationship between the degree or type of control and the development of the renal disorder, the pathogenesis of the syndrome in the light of recent experimental laboratory and clinical studies, diagnostic criteria and treatment are discussed.

Robbers, H.; and Rümelin, K. (*Inn. Abt. des Fürst-Carl-Landeskrankenhauses, Sigmaringen, Germany*): DOES RENAL DIABETES DEVELOP INTO TRUE DIABETES MELLITUS? Deutsche med. Wchnschr. 78:1321-23, Sept. 25, 1953.

Observations were made in 60 cases of renal glycosuria for periods ranging from 2 to 36 years. In the majority of cases, the observation period was more than 8 years. Following results were established:

1. Sugar elimination remains fully constant over many years. In rare cases, it disappears completely.

2. The blood sugar level and glucose tolerance curves remained at all times within normal standards.

3. The subjective symptoms complained of were mainly functional and become rarer with increasing age.

4. The development of renal glycosuria into true diabetes is rejected. In rare instances an inherited disposition to renal diabetes and diabetes mellitus may occur in one and the same person. Then, independently of each other, true pancreatic diabetes may become manifest in the course of renal diabetes. (German)

Root, Howard F. (*Joslin Clinic, Boston, Mass.*): INSULIN RESISTANCE. Pennsylvania M. J. 57:1098-99, November 1954.

The term "insulin resistance" has been used in reports of many individuals in whom excessively large amounts of insulin have been required for treatment of diabetes or other purposes. The existence of diabetes is not a prerequisite for resistance, since it is well known that in the insulin treatment of schizophrenia certain patients require increasingly large doses of insulin to produce the hypoglycemic coma desired. There is a considerable group of diabetic patients who have developed resistance without acute complications, requiring insulin for long periods of time in amounts from two hundred to several thousand units a day. In some cases, autopsy has revealed complicating chronic conditions, but in a considerable number no such complicating lesions have been demonstrated. Lerman, Lowell, and others have suggested that insulin resistance is related to the development of antibodies and that the degree of resistance parallels their concentration. Insulin is a poor antigen, but it is possible that in some patients accompanying infections may alter the antibody mechanisms.

One case of insulin resistance, studied by Root, Evans, Irvine and others, was that of an elderly Jewish woman, formerly requiring 10 units of insulin, who developed an insulin requirement of 2,000 units daily. It was found that a moderate dose of insulin given by vein had a more marked effect upon the respiratory quotient than a much larger dose given under the skin. Alteration in the transport of insulin was suspected. Accordingly, a special insulin compound with radioactive iodine was administered to this patient, together with a group of nonresistant diabetics and normal controls. Using a Geiger counter, the results indicated that insulin left the site of injection in this patient more slowly than in normal individuals or in diabetic patients without evidence of resistance. In this same case, in which the serum also contained antibodies to insulin, an attempt to use insulin derived from human pancreas did not alter the condition.

In the treatment of insulin resistance, the use of preparations of insulin of high concentration up to 500 units per cc. was begun many years ago. The use of large doses of "regular" or unmodified insulin is accompanied by a marked prolongation of the duration of action, so that a single large dose of regular insulin once daily before breakfast may have an effect lasting throughout 24 to 30 hours.

Rubin, Leonard; and Aladjem, Frederick (*Donner Lab., Div. of Med. Physics, Univ. of California, Berkeley, Calif.*): SERUM LIPOPROTEIN CHANGES DURING FAST-

ING IN MAN. Am. J. Physiol. *178*:263-66, August 1954.

Fasting for 4 or 5 days resulted in a significant elevation of the low-density serum lipoprotein concentrations of five of six healthy volunteers. Three were men aged 23 to 29; three were women aged 23 to 43. The single individual who exhibited no increase had been on low fat (15 gm.), low cholesterol (200 mg.) diet for over 2 years prior to the experiment. The concentration of high-density serum lipoproteins was not significantly altered during the period of fasting. Restoration of normal levels occurred within 24 hours of resumption of a normal diet. Sucrose ingestion at the end of the period of fasting did not significantly change serum lipoprotein concentration in 3 hours.

Sauer, Heinrich; and Düssler, Albrecht (*I. Med. Univ.-Klinik, Hamburg, Germany*): ON THE DISEASE PICTURE OF DIABETIC POLYNEURITIS AND ITS TREATMENT WITH VITAMIN B_{12}. Deutsche med. Wchnschr. 79:1046-48, June 25, 1954.

The treatment of diabetic neuritis with vitamin B_{12} is reported in 18 cases; 15 were subjectively improved and free of symptoms, 3 remained unimproved, 2 of these in spite of high doses. Uninfluenced were reflex deficiencies, reduced touch and pain sensations and vegetative disorders. A dosage of 30 to 60 gamma daily for one to two weeks was recommended by the authors; smaller quantities were considered generally sufficient for relapses. (German)

Schliack, Volker (*Diabetikerheim Garz und Karlsburg, Germany*): DIABETES PROBLEMS: RESEARCH ON THE FREQUENCY, AGE DISTRIBUTION, MANIFESTATION AGE AND MANIFESTATION CONDITIONS OF DIABETES MELLITUS. Deutsche med. Wchnschr. 79:855-56, May 21, 1954.

The article presents the actual composition of the diabetic population according to age and sex, in Leipzig, East Berlin, West Berlin, and Vienna; the influence of war and postwar nutrition on diabetes morbidity; the age incidence in 11,294 cases of diabetes; the frequency of diabetes (series examination of the population). The main age of highest incidence is the sixth decade in life; in the female sex there is a preponderance this side of the fortieth year of age. Due to the deficient nutrition of the war and postwar periods the sex ratio was temporarily changed. To be pointed out particularly is the large number of unrecognized cases: In a systematic examination of the total population, five persons were found to have previously undiagnosed diabetes for each case of known diabetes. (German)

Schliack, Volker (*Diabetikerheim Garz/Rügen und Karlsburg, Germany*): ON THE QUESTION OF INSULIN LIPODYSTROPHY IN TUBERCULOUS DIABETICS. Klin. Wchnschr. *31*:1044-46, Nov. 15, 1953.

In a large number of nontuberculous diabetic patients the author found lipodystrophy in 27 per cent, the atrophic form in a total of 10 per cent. The incidence among women was greater. Among 100 stationary tuberculous diabetics the author saw the changes in about the same frequency (20 per cent). In form, extent, sex or age predilection no differences were evident. (German)

Silbert, Samuel; Haimovici, Henry (*Montefiore Hosp., New York, N.Y.*): CRITERIA FOR THE SELECTION OF THE LEVEL OF AMPUTATION FOR ISCHEMIC GANGRENE. J.A.M.A. *155*:1554-58, Aug. 28, 1954.

Within recent years, the management of patients with gangrene, ulceration, and infection of the extremities associated with obliterative arterial disease and diabetes has undergone a conservative trend. Chief among the factors responsible for the better prognosis of both limb and life are the use of antibiotics and better understanding of the peripheral vascular problems. Experience accumulated in the past decade with the use of these agents has shown that amputations below the knee at the metatarsal and toe levels are successful in a large number of cases. This experience indicates that a more conservative attitude is now fully justified.

Choice of the proper level for amputation depends on careful evaluation of local factors and the patient's general condition. Chief among the local factors are the extent of gangrene or ulceration, the degree of infection, the condition of adjacent areas, the degree of arterial impairment, and the severity of pain. There are five suitable levels for amputation of the leg. Conservative amputations are advocated. Single toe or transmetatarsal amputation permits rehabilitation without the use of a prosthesis. Supramalleolar amputation offers great advantages in patients in poor general condition because of its rapid execution and its minimal surgical risk. The

advantages of midleg over thigh amputation are lower operative mortality, better prospect of rehabilitation, and absence of persistent stump pain.

Silver, Gershom B. (*Veterans Hosp. and Hosp. for Chronic Illness, Rocky Hill, Conn.*): ANURIA: CASE REPORT. Connecticut M. J. *18*:667-61, August 1954.

A case of total anuria in a 67-year-old male due to lower-nephron nephrosis which was presented at a medical conference is discussed from the diagnostic and therapeutic points of view. The blood sugar was 174 mg. per 100 cc. It was pointed out, however, that any patient with anuria might present an elevation in blood sugar without diabetes. The test of the blood plasma for acetone bodies was negative. This, therefore, ruled out diabetic acidosis. An acetone test of plasma or serum is a more reliable index than a test for ketonuria since renal failure in association with diabetic acidosis may result in disappearance of ketonuria.

Soskin, Samuel (*Univ. of Calif., Los Angeles, Calif.*): DIABETES—ITS RELATION TO INDUSTRY. Indust. Med. *23*:106-07, March 1954.

As to the nature of the employment suitable for the insulin-treated diabetic, the general restrictions depend upon the fact that he must constantly maintain a midposition between inadequate control of his diabetes on the one hand, and hypoglycemic reactions on the other hand. This is usually not difficult to accomplish when insulin administration, food intake, and physical exercise are routinized and are balanced against each other in a predictable fashion, day after day. Hence diabetics should work the same hours on a steady shift; or, if they must work on a rotating schedule, the "graveyard shift" from midnight to 8:00 A.M. should be avoided. Furthermore, the work should not entail emergencies which require the diabetic significantly to delay or omit an injection of insulin or a meal; and the work should not be so variable in its demands for physical exertion that it requires considerable muscular work on one day and little on another.

The particular jobs in a given plant that are suitable for the diabetic should be selected with regard to (a) safety to himself, (b) safety to others, and (c) conservation of the employer's property. Because of the occasional occurrence of hypoglycemic reactions without warning, even in well-controlled diabetics, it is unwise to employ them on moving machinery which might be hazardous to the unwary operator, or to require them to work on platforms or ladders above the ground floor level. It should also be remembered that diabetics may have a somewhat greater than normal susceptibility to upper respiratory and skin infections. Hence one should avoid exposure to skin irritants, to dust-laden air, and to conditions leading to wet shoes or bruised feet, in order to minimize the possibility of preparing the way for boils and carbuncles, pulmonary tuberculosis, or gangrene of the feet.

Stetten, Marjorie R.; and Stetten, DeWitt, Jr. (*Div. of Nutrition and Physiol., Public Health Res., Inst. of the City of New York, Inc., New York, N. Y.*): A STUDY OF THE NATURE OF GLYCOGEN REGENERATION IN THE INTACT ANIMAL. J. Biol. Chem. *207*:331-40, March 1954.

Enzymic degradation of glycogen samples was employed as a means of studying the nature of glucose replacement in different portions of the glycogen molecule. Radioactive glucose was injected intraperitoneally into rats and, after various time intervals, glycogen was isolated from liver and carcass. Each glycogen sample was exhaustively digested with B-amylase and the distribution of C^{14} between the maltose (periphery) and the limit dextrin obtained was determined. B-amylase is an enzyme which attacks the nonreducing ends; it yields maltose from the unbranched peripheral tier of the glycogen molecule and to a degree dextrin, stable in B-amylase, which represents the central core of the glycogen molecule.

According to the authors, the findings obtained show that glycogen, although yielding only glucose upon total hydrolysis, is metabolically inhomogeneous. Glycogen turnover in vivo is not merely a replacement of existing molecules by newly formed glycogen molecules. Glucose residues situated peripherally in the glycogen molecule are renewed faster than those more centrally located, and this contrast is more striking in muscle than in liver.

The conclusions are discussed in relation to what is known about the mammalian enzymes concerned with glycogen formation and destruction.

Tarail, Robert (*Roswell Park Memorial Inst., Buffalo,*

N. Y.): DIABETIC ACIDOSIS. Am. J. Clin. Nutrition *2*: 272-73, July-August 1954.

The author contends that success in the treatment of diabetic coma could be greatly improved by attention to two vital factors:

(1) Organization of a competent team responsible for all cases in any institution.

(2) Following one of the many reasonable systems of management of the disorder.

Thal, Alan; Brackney, Edwin (*Dept. of Surg., Univ. of Minnesota Med. Sch., Minneapolis, Minn*): ACUTE HEMORRHAGIC PANCREATIC NECROSIS PRODUCED BY LOCAL SHWARTZMAN REACTION. EXPERIMENTAL STUDY ON PANCREATITIS. J.A.M.A. *155*:569-74, June 5, 1954.

Fulminating hemorrhagic pancreatitis was produced in the rabbit and the goat by means of sensitization of the pancreatic blood vessels to bacterial products. This was accomplished by introducing meningococcic or Escherichia coli endotoxin into the pancreatic duct. Rapid diffusion of bacterial toxin through intact ductal walls was repeatedly observed. Histological studies uniformly showed capillary and venular hyaline thrombosis.

Thosteson, George C.: DIABETES AND PREGNANCY. Harper Hosp. Bull. *11*:245-47, Nov.-Dec. 1953.

Primiparae and multiparae with diabetes of short duration may be candidates for vaginal delivery where there are no obstetrical contraindications and the conditions for induction appear suitable. Patients with diabetes of over five years' duration are candidates for elective cesarean section. The results with hormonal therapy were inconsistent and unimpressive. Factors assuring the diabetic patient a successful gestation appear to be adequate control of diabetes and careful timing of delivery, accomplished through the close co-operation of internist, obstetrician, and pediatrician.

Warming-Larsen, Aage (*Medicinsk Afdeling, Blegdamshospitalet, Copenhagen, Denmark*): KETONE METABOLISM IN OBESITY II. Acta med. scandinav. *150*:47-52, Sept. 11, 1954.

In 42 obese and 25 normal persons, the degree of inanition ketosis was determined. The obese patients showed significantly wider variations than the normals, which is in good agreement with the findings of other authors in small numbers of patients. The group of obese patients with failing starvation ketosis represents a metabolic problem; they might represent a possible endocrine group with incipient diabetes mellitus or simply a fat-adapted group like the Eskimo race.

Watts, Daniel T. (*West Virginia Univ. Sch. of Med., Dept. of Pharmacol., Morgantown, W. Va.*): INHIBITION OF ETHER HYPERGLYCEMIA BY ADRENERGIC BLOCKING AGENTS. Anesth. & Analg. *33*:343-45, September-October 1954.

It has been shown that 0.15 mg. per kg. of hydergin, an equimolar mixture of dihydroergokryptine, dihydroergocristine, and dihydroergocornine, completely abolishes ether hyperglycemia in rabbits. Dibenamine, 50 mg. per kg. and priscoline, 10 mg. per kg. had no effect on ether hyperglycemia.

Wilens, Sigmund L. (*Dept. of Pathol., Bellevue Hosp., and the Dept. of Pathol., New York Univ., Bellevue Med. Center, New York, N. Y.*): THE RELATION OF DIABETES TO ATHEROSCLEROSIS. New York S. J. Med. *53*:2451-52, Nov. 1, 1953.

The author points out that in view of the prevailing disagreement as to what factors promote the development of atherosclerosis in man it is all the more remarkable that at the present time there is almost universal agreement that diabetes tends to accelerate this disease. The relation of diabetes to atherosclerosis is discussed from several viewpoints including: the discrepancies in the incidence of atherosclerosis in experimental as well as various clinical types of diabetes, the disturbed lipid metabolism in diabetes, and the tendency for lipid accumulation to form not only in large arteries but in very small branches in various organs not ordinarily involved. Closer attention to the blood lipid levels is suggested as a possible means of controlling some of the late complications of diabetes.

EDITORIALS

INTERLINGUA IN DIABETES

In this issue of DIABETES, summaries of original scientific articles are presented in Interlingua. DIABETES now follows the example already set by ten other medical journals in attempting to provide for foreign readers easy access to an understanding of its contents.

Interlingua is an international or supranational language constructed by the collection of words common in the various European languages and their synthesis in a systematic pattern. "Interlingua is French modified by Spanish, English, Italian—; it is Italian modified by Portuguese, German, Latin—; it is Latin modified by French, English, Spanish—; it is the common language of western civilization—." The use of Interlingua is sponsored by Science Service, The Institution for the Popularization of Science organized in 1921 as a non-profit corporation with trustees nominated by the National Academy of Sciences, the National Research Council, the American Association for the Advancement of Science, the E. W. Scripps Estate, and the journalistic profession. The Interlingua Division of Science Service is headed by Dr. Alexander Gode.

In addition to its employment in medical journals, the service potential of Interlingua was strikingly demonstrated in the program of the Second World Congress of Cardiology which met in Washington, D.C., last September. This publication contained Interlingua summaries totaling 85,000 words and was placed in the hands of more than 3,000 cardiologists representing some 50 different nations.

With Interlingua summaries available in DIABETES, the foreign reader whose knowledge of English is limited should be enabled to learn from quickly scanning the summary the meaning and significance of every article. He can then select for careful reading and perhaps laborious study those which are interesting and important from his point of view. It is hoped that this innovation will promote more effectively the usefulness of the Journal beyond the limits of English-speaking countries.

PROGNOSIS OF DIABETES IN RELATION TO TREATMENT

The life expectancy of diabetics has more than trebled during the past 34 years.[1] Coma as a cause of death is becoming rare but in its place, degenerative changes in the blood vessels in the kidneys, heart, eyes, extremities and elsewhere are appearing with increasing frequency. These vascular changes seem to be specifically diabetic. Lundbaek[2] in his monograph on "Long-term Diabetes" summarizes ably the basis for the distinction from ordinary arteriosclerosis. It seems reasonable to designate as *late diabetic syndrome,* manifestations which apparently result from long-term diabetes mellitus and to reserve the term *diabetic complications* for conditions not genetically related to diabetes, such as carbuncle, tuberculosis, pneumonia and others. The cause of the late diabetic syndrome, whether lack of insulin, suprarenal or other hormonal dysfunction, and/or a disorder of lipid metabolism, is still unknown. For the patient, however, the most important question is—can it be avoided?

Some authorities consider the late diabetic syndrome to be the unavoidable consequence of diabetes of long duration and believe insulin as well as diet to be of no value to prevent or combat it. Hereditary constitution or a hitherto unknown pancreatic factor are said to determine how soon it will develop. Others are more hopeful. The series of cases selected for award of the Joslin "Quarter Century Medal" is significant. The medal is awarded to persons who have had diabetes for twenty-five years or more and have been found free from late complications. Since all individuals who have received the medal are said to have had good control of diabetes at least during the first years, it can be assumed that there is a relation of cause and effect between good control and a favorable course of the disease. As long as there is no better explanation, there is not only justification but an obligation to base treatment on this working hypothesis. This opinion is strengthened by the com-

parison of diabetics who have had good control of the condition with others who have had poor control. Evidence from various sources[3-6] shows a lessened incidence of late symptoms for the former group. It must be conceded, however, that even in cases receiving excellent control, retinopathy has not always been avoided.

My associates and I[7, 8] have studied the present condition of 103 patients who have had diabetes for 20 years or more. In agreement with the previous observations made elsewhere, we have found in Switzerland that the severity of the disease (as indicated by the insulin dosage required), and the kind of insulin (regular, slowly acting, combinations) had no apparent influence on the development of late symptoms. On the other hand, the prognosis was affected greatly by the age of the individual and the degree of control of diabetes.

Approximately one-fifth of cases were practically free from late symptoms. One fifth showed slight and three-fifths showed marked vascular changes. Of 28 diabetics who had onset of the condition before the age of 30, 15 showed no vascular changes, and 3 minimal changes. Of 75 older diabetics, 52 showed advanced degenerative changes. Of 21 diabetic patients in whom the disease had been kept under continuous good control, only one had advanced and 9 had minimal vascular lesions. On the other hand, of 32 patients who had never had good control of the disease, only 2 escaped late vascular lesions; 2 others had minimal symptoms and 28 had the typical late diabetic syndrome. Of the 2 poorly controlled cases in which there was freedom from vascular degeneration, one was a poor farmer in the mountains of Switzerland who for economic reasons was compelled to exist on a low-caloric food intake while performing hard manual labor; he used so much insulin that he was barely free from hypoglycemia. In the other case, the patient was a wealthy farmer from South America who led an active life spending much of his time on horseback; he was accustomed to eating much meat and using insulin liberally.

Although it cannot be determined with absolute certainty that our treatment with diet and insulin can prevent the late diabetic syndrome, I am convinced that good control of diabetes still offers the best opportunity of avoiding or at least retarding its future development. The few cases in which there is exceptionally little tendency to show progression, and the favorable course of juvenile diabetes during the first eight to ten years of treatment with insulin, should not encourage a careless attitude towards control of glycosuria and hyperglycemia. A pediatrician who is unable to follow his juvenile cases may not be fully aware of the late complications appearing when his patients have outgrown their childhood. A physician who begins the treatment of a young person with diabetes must accept responsibility for the welfare of the individual for twenty years and more in the future, even if the ultimate result of his treatment cannot be foreseen. The therapy which at present seems to offer the best outlook should be based on good control with diet, insulin and exercise.

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GEORG R. CONSTAM, M.D.
Consultant for Diabetes, Medical Policlinic
University of Zurich, Switzerland

Adolf Kussmaul

David Adlersberg, M.D., New York*

Adolf Kussmaul was one of the great physicians of the second half of the 19th century, one of the pioneers who broke the "unnatural alliance" which medicine had formed with philosophical speculation and placed scientific medicine rightly among the biological sciences. He considered himself most fortunate to have passed through life as a child of the 19th century. "No other century is comparable with it in enthusiasm and ability to penetrate the secrets of nature, none has advanced the general welfare and made life more pleasant with the same measure of inventive spirit, and finally, none has scattered more decisively and victoriously the chains of slavery in all parts of the world."

Adolf Kussmaul's grandfather was a "feldsherer" in the little country village of Soellingen, Germany, and had the official title "chirurgus." Kussmaul's father, born in 1790, served as an army surgeon (Wundarzt) for five years and then continued the study of medicine. His clinical notes compiled in 1819 and 1820 are of interest in that they depict the status of clinical medicine of the time based on philosophical deductions: "Liver and spleen are two oppositely-placed poles, as are also iron and mercury. Iron is the stiffest and most solid, mercury the softest and most penetrable of all metals. From this, a theory regarding the value of iron in diseases of the spleen can be deduced. Just as mercury is helpful in diseases of the liver, so iron is in the diseases of the spleen."

Adolf Kussmaul was born Feb. 22, 1822, in Graben, near Karlsruhe, Germany. The origin of the rather unusual name, Kussmaul, ("kiss snout"), cannot be ascertained definitely. Adolf Kussmaul considered himself to be a descendant of the great physician Oribasius ("os," the mouth; and "basium," the kiss). Others believed that Oribasius was a latinized Greek word and meant "hill-goer" or "hill-man." Some interpreted the name Kussmaul as being derived from the old German "Kusso" (the good one) and "Mulo" (the energetic one). In his autobiography, Kussmaul recounts many episodes of embarrassment and amusement caused by his name. A prominent lady to whom he was introduced early in his career asked him to repeat the name and then said simply: "No. It is impossible. No one can have such a name." One of his teachers advised him on several occasions to have his name changed. Kussmaul politely rejected such advice, emphasizing that his family came "from the oldest medical nobility."

Kussmaul completed his medical studies in Heidelberg. The medical school of the University of Heidelberg became a growing center of scientific research and attracted many promising young men. Henle, the anatomist, was one of the leading rebels against philosophical medicine. His goal was "rational medicine" based on exact anatomical observations. Henle was editor of the journal *Zeitschrift fuer rationelle Medizin* and of the *Handbuch der rationellen Pathologie*. In order to understand the medical milieu of that time one must recall that diseases were diagnosed according to symptoms only. Thus, the common clinical diagnoses were dropsy, jaundice, cyanosis, hyperpyrexia, apoplexy and dysentery. Kussmaul had great admiration for Henle and for another teacher, the obstetrician Naegele, one who placed obstetrics on a sound anatomical and physiological basis. During the last year of his study (1845) Kussmaul wrote a paper on the anatomical, physiological and pathological nature of the color changes in the fundus of the eye. Through this paper he was awarded the Karl Friedrich Gold Medallion, to the great satisfaction of his father. He worked hard on the structure of an ophthalmoscope, but it was reserved for Helmholtz to fulfill this dream.

Kussmaul's postgraduate work brought him to Vienna and Prague. In Vienna, Rokitansky, Hebra and Skoda were his teachers. Rokitansky's autopsies, Hebra's lectures on skin diseases and Skoda's correlation of auscultation and percussion with autopsy findings were of great interest to Kussmaul. But his respect went to Semmelweis who was then engaged in his work on the causes of puerperal fever. Kussmaul was permitted to practice in

*Assistant Clinical Professor, College of Physicians and Surgeons, Columbia University; Associate Attending Physician for Metabolic Diseases, Mount Sinai Hospital, New York City.

the obstetrical wards, a privilege seldom granted. In Prague, Kussmaul worked under an outstanding teacher, Johannes Oppolzer. Upon his return to Germany he served in the army as a military surgeon. He then settled for four years in Kadern, a picturesque small town in the Black Forest, where he developed an extensive and profitable general practice.

In spite of heavy routine work, long working hours and sleepless nights, Kussmaul found time to continue his scientific work. Based on his observations in country practice he published papers on acute rheumatism, dysentery, stomatitis septica, typhoid fever and phlebitis hepatica. This phase of his life was terminated by a severe protracted disease "meningitis lumbalis." His feet were senseless and the bladder was paralyzed; the symptoms of paraplegia are suggestive of poliomyelitis. The paralysis of the bladder subsided first but it took many months before Kussmaul could leave his bed and a number of years before he had the normal use of his legs.

Having recovered from this disease, Kussmaul decided to change his life radically. He gave up country practice and made preparations for the academic career which had always been his real ambition. Kussmaul learned a good lesson from his sickness. It made him become, in his own words, "an understanding physician." He often recited to his students the lessons of his disease. He wished them to pass through a serious disease in order to become good physicians. They would then understand what care, kindness and tenderness mean to a suffering patient. He insisted that his students should learn the particulars of nursing, the making of a bed, the preparation of food. He laid great stress upon the moral and mental influence of the physician upon his patient.

With his modest savings he pursued the study of the scientific branches of medicine. He was attracted to Wuerzburg by the great personality of Virchow. In 1856, he was admitted to the University of Heidelberg as an instructor (privat-dozent) and was appointed in the following year professor extraordinarius. He devoted the second of his autobiographies to this period of his life. In 1859, he was called to the chair of medicine in Erlangen, in 1864 in the same capacity to the University of Freiburg, and in 1876 to the new medical school of the University of Strassburg. In 1888, he retired from his academic positions and returned to his beloved Heidelberg where he spent the remainder of his life.

Kussmaul's scientific contributions extended into many fields of medicine. Some of his classical papers exerted a deep influence upon the development of medicine. His famous essay "Studies on the Psychology of the Newborn" was delivered as the opening address before the Medical Faculty of the University of Erlangen. Published in 1859, it was republished in 1885 and 1896. Another classic is his paper on "Disorders of the Speech." He published pioneering work on rigor mortis, mercury poisoning, osteomyelitis, embolism of the mesenteric arteries, paradoxical pulse and periarteritis nodosa. He gained great popularity by the use of the stomach tube in the treatment of pyloric obstruction. Although Kussmaul did not invent the stomach tube, as some erroneously believe, he carefully described the indications and contraindications for its use. He predicted so many years ago "that the keener intellects of future generations will undertake in such case to resort to gastrotomy, stomach fistula or enlargement of the pyloric opening by means of a knife or tube, in order to obtain radical results."

Closely associated with his work on the use of the stomach tube were observations of the esophagus and stomach in which the esophagoscope and gastroscope were employed (probably the endoscope of Désormeaux). He used the instrument first in a professional sword-swallower. The light source was too weak to permit reliable observation. His work as well as that of his students gave important impetus to the development of modern gastroenterology. It included basic observations on gastric secretion, motor activity of the stomach, treatment of ileus and treatment of gastric ulcer.

Kussmaul's last publication in Freiburg was concerned with diabetes mellitus ("Zur Lehre vom Diabetes Mellitus," 1874). He observed in three diabetics a hitherto undescribed terminal symptom complex which he called "diabetic coma." The striking features were dyspnea of a special character associated with rapid pulse and general debility. The description of the dyspnea reads as follows:

"*A peculiar type of dyspnea.* In this type of dyspnea there is not the least suggestion, as is so common in all other types, that the passage of air to or from the lung has to combat obstruction; to the contrary, it passes in and out with the greatest of ease. The thorax expands noticeably in all directions without a pulling-in of the lower end of the sternum or of the intercostal spaces. (In the last minutes of life when I could no longer examine the patients it may have been different.) The complete inspiration is followed by a likewise complete expiration. In the deepest parts of the lungs, one can notice perfectly clear, loud and distinct vesicular breathing; and yet everything is indicative of extreme air hunger, such as the discomfort of angusty of which the patient complains, the extreme activity of the respiratory

muscles, and the loud noise that the powerful inspirations and more so the expirations make as the air passes through the larynx. A true stridor, however, never exists. . . . . The marked contrast between the extreme general weakness of the patient and the powerful respiratory movements is a striking peculiarity of this picture."

In Kussmaul's opinion, the dyspnea of diabetic coma was not caused by anoxia of the respiratory centers nor by the accumulation of carbon dioxide in the blood. Its origin was probably an intoxication related to the chemical metabolic disorder in diabetes. No definite statement could be made as to the nature of the toxic agent causing probably both the dyspnea and the coma.

Kussmaul performed clinical and experimental studies on the effects of acetone. He found its action in rabbit and men not as intensive as that of chloroform or ether but stronger than that of alcohol; considerable doses could be tolerated without poisoning. Although he was sceptical as to the role of "acute acetonemia" in the etiology of diabetic coma, he found it quite possible "that prolonged acetonemia may result in chronic intoxication, especially in a weakened nervous system. This intoxication may produce sudden acute symptoms in a manner similar to the delerium tremens of the chronic alcohol addict."

The careful description of the clinical manifestations of diabetic coma by Kussmaul, the experimental work performed to support and explain the clinical findings, especially the dypsnea, and the conservative interpretation of the observations is generally considered a classical contribution to the knowledge of diabetes mellitus.

When over 75 years old, Kussmaul wrote his celebrated autobiography *Youthful Recollections of an Old Physician.* This beautiful book depicts the genius and great personality of Kussmaul. It has been reprinted in many editions and read by generations of physicians. Another autobiography, *My Instructorship in Heidelberg,* although incomplete, was published after his death by his son-in-law, the surgeon, Vincenz Czerny. Kussmaul also started at this age research work and a monograph on epilepsy which remained unfinished. In his younger years he was very fond of reading and writing poetry. In his later years he found his mislaid poems among old books and published them under the title of *Poetic Juvenile Sins of Dr. Oribasius.*

In the early morning of May 28, 1902, three months after his eightieth birthday, Adolf Kussmaul died suddenly, probably of a myocardial infarction. The foreword to his autobiography written as a poem in his old age reflects his great harmonious personality (translated by T. H. Bast):

If in your heart you must sorrow bear
And the burden of old age days
Invite as the guest for your burdens to share
The remembrance of your youthful ways.

BOOK REVIEW

STANDARD VALUES IN NUTRITION AND METABOLISM: *Edited by Errett C. Albritton, A.B., M.D., Fry Professor of Physiology, The George Washington University. Prepared under the direction of the Committee on the Handbook of Biological Data, American Institute of Biological Sciences and the National Research Council, Air Research Development Command, United States Air Force, Wright-Patterson Air Force Base, pp. 380. McGregor and Werner, Inc., Dayton, Ohio, July 1954.*

This volume is the second part of a handbook of biological data. It represents one of the best efforts to collect and tabulate essential data relating to the field of nutrition and metabolism. More than eight hundred individual scientists have contributed towards making it the valuable compendium that it is. This book is essential to every science reference library throughout the world. It encompasses the nutritional and metabolic requirements of both plant and animal life, including the human. It presents excellent summaries of metabolic pathways, oxygen requirements and energy exchange values. The data are substantiated by the endless number of references to the original literature. The index is so arranged that there is no difficulty in finding reference material.

The review process to which the material has been subjected is designed to eliminate all questionable and controversial material. The committee hopes that the data as presented represent the acceptable material which can be considered established. The tables present the data with due respect to biological variations and present not only representative values but also the ordinary range of variation of the variables.

Scientists all over the world will be grateful to the Committee on the Handbook of Biological Data and to the Wright Air Development Center, U. S. Air Force, the Office of the Surgeon General, Department of the Army, the Office of Naval Research and the Division of Biology and Medicine of the Atomic Energy Commission for their judgment in authorizing its publication.

Organization Section

The American Diabetes Association has been engaged in the activities of the International Diabetes Federation and has worked actively toward its development since the first IDF Congress held in Leiden, Holland, in July 1952. Arrangements for official ADA membership in the Federation were completed recently when our Executive Committee and Council voted acceptance of the IDF's Constitution and Bylaws. This document is published below.

Many members of the Association have made plans to attend the Second Congress of the International Diabetes Federation to be held in Cambridge, England, July 4-8, 1955. A brochure containing information about reservations and so forth may be secured from the National Office of the American Diabetes Association.

INTERNATIONAL DIABETES FEDERATION
Federation Internationale du Diabete
The Hague

CONSTITUTION

Article I

NAME

The organization shall be a federation of national diabetes associations, and its name shall be the "International Diabetes Federation" (Fédération Internationale du Diabète). It may also be referred to as the "I.D.F." or "F.I.D."

Article II

LANGUAGES

The official languages shall be English and French.

Article III

PURPOSES

The objectives of this Federation are to further the acquisition and dissemination of useful and accurate information regarding diabetes mellitus and to undertake such activities as will improve the physical and socio-economic welfare of persons afflicted with the disorder.

To these ends it is the purpose of the Federation to promote the free exchange of knowledge with respect to diabetes mellitus; to improve the standards of treatment of diabetes mellitus; to promote medical and other related scientific research, as well as statistical and socio-economic investigation pertaining to diabetes mellitus; to develop educational methods designed to give diabetic patients a better understanding of their disease; to educate the general public in the early recognition of diabetes mellitus and in the importance of medical supervision of its treatment; and to encourage the creation of national diabetes associations, which it is believed will assist in fulfilling the objectives of the Federation.

Further, it is the aim of the Federation to take all such measures within its ability, necessary to achieve the above objectives, and in particular to organize congresses and meetings pertaining to the scientific and medical aspects of diabetes mellitus, as well as the social and economic problems of that disorder.

Article IV

TYPE OF ORGANIZATION

The Federation shall be conducted without profit and no part of any income of the Federation shall be applied to the benefit of any member-association, official or delegate, except for actual services rendered and only then upon authorization of the General Council.

Article V

OFFICES

The Federation shall have and continuously maintain an Executive Office and may have regional or branch offices.

Article VI

MEMBERSHIP

Section 1: *Membership classification.* Membership in the Federation shall consist of national Diabetes Associations in each country in which there are suitable and representative national organizations.

Section 2: *Election to Membership.* Membership in the Federation shall be determined by the General Council upon written application of a national Diabetes Association.

Section 3: *Voting Rights.* Each member organization is entitled to two votes at the General Council. (See General Council provision, article VIII). Voting by written proxy is permissible.

Section 4: *Termination of Membership.* Any member may resign six months after a written notification of resignation, but such resignation shall not relieve the afore-mentioned member of any financial obligation theretofore accrued and unpaid, except by specific action of the General Council.

The General Council by affirmative vote of two-thirds of all its members may suspend or expel a member association for action contrary to the purposes and/or the best interests of the Federation. Such action may be taken only after appropriate hearing and consideration.

Article VII

MONETARY CONTRIBUTIONS

Each national member association of the Federation shall make monetary contributions as equitably determined by a two-thirds majority written vote of the General Council.

Article VIII

GENERAL COUNCIL

Section 1: *Authority.* The General Council shall direct the policies and the activities of the Federation.

Section 2: *Membership Qualification and Tenure.* The General Council shall be composed of one medical (or allied sci-

ence) delegate and one lay delegate from each national member association, and all officials of the Federation, each delegate and official being entitled to one vote.

Section 3: *Meetings.* A regular meeting of the General Council shall be held at least once every three years, approximately at the same time as the Federation's Congress.

Special meetings of the General Council may be provided by resolution of the General Council. Further, such a meeting may be called by the President with approval of the Executive Board, or upon written request of one-third of the total of the membership of the General Council.

Section 4: *Notice.* Notice of any regular or special meeting of the General Council must be given in writing to each member association and individual officials at least 90 days prior thereto.

Section 5: *Quorum.* One-third of the total number of members of the General Council shall constitute a quorum.

Section 6: *Naming of Delegates.* The names of each national association's delegates shall be forwarded to the Secretary-Treasurer.

Section 7: *Vacancies.* Vacancies to the General Council shall be filled by the member associations within at least three months from the date of vacancy. If a delegate is temporarily unavailable, the respective national association should appoint a substitute to serve.

Section 8: *Selection of Executive Board.* (Officials). It shall be the responsibility of the General Council to elect the officials of the Federation from members of the General Council.

Section 9: *Time and Place of Congresses.* The General Council shall be responsible for establishing the date and place of the Federation's Congresses.

Section 10: *Receipt of Reports and Statements.* The General Council shall receive the reports of the Executive Board and other reports and statements of the councils, committees and boards.

Article IX

OFFICIALS

Section 1: *Classification.* The officials of the Federation shall be a President, one or more Vice-Presidents and a Secretary-Treasurer. The Federation may also elect one or more Honorary Presidents.

Section 2: *Election of Officials.* The officials shall be elected from the present or past membership of the General Council by the General Council at a duly constituted regular meeting. If election of officials cannot be held at a regular meeting, it shall take place as soon thereafter as possible and incumbent officials shall serve until their successors have been duly elected.

Section 3: *Tenure of Office.* The term for each official shall be from one Congress to the following Congress, or a period of approximately three years.

Section 4: *Vacancies.* A vacancy in the office of the President, Vice-President(s) or Secretary-Treasurer shall be filled by action of the remaining membership of the Executive Board for the unexpired term of office. The appointment shall be made from the present or past membership of the General Council.

Article X

EXECUTIVE BOARD

Section 1: *Members.* The Executive Board shall consist of the principal officials (President, one or more Vice-Presidents and Secretary-Treasurer) of the Federation. If any of these are not available, the President may appoint a substitute(s) from the membership of the General Council.

Section 2: *Responsibilities.* The Executive Board shall be charged with the responsibilities to act for the General Council between meetings and in the interest of expediency may consider and review all matters of policy. Further, the Executive Board acting collectively may take any executive action deemed necessary to fulfill the objectives of the Federation. The Executive Board shall be responsible to the General Council and shall submit a report of all action taken at the next duly constituted meeting of the General Council.

Article XI

ADOPTION OF CONSTITUTION

This Constitution may be adopted by a three-fourths majority of the organizing national diabetes associations or their duly authorized representatives. Ratification of the Constitution must be made in writing and/or by written vote by the afore-mentioned representatives after submission of proper credentials.

Article XII

AMENDMENTS TO CONSTITUTION

This Constitution may be altered, amended or repealed by a two-thirds written affirmative vote of members of the General Council at a duly constituted meeting, providing that the proposition so to change the Constitution has been previously submitted in writing to members of the General Council 90 days prior to the meeting at which final action is to be taken.

BYLAWS

Article I

Location of the Executive Office. The Executive Office is to be located in the Netherlands. (See article VIII, section 9 of the Constitution.)

Article II

Monetary Contributions. The monetary contributions of each national member association shall be made on an annual (calendar year) basis.

Further, such contributions of each national member association shall be based on per capita voting membership of each such association and shall be computed at the rate of 10 cents Dutch currency or its equivalent annually. (See article VII of the Constitution).

Article III

Accounts. Section 1: *Fiscal Year.* The Secretary-Treasurer shall keep accounts of all income and expenditures of the Federation, based on a calendar year, January 1 through December 31.

Section 2: *Audits.* At least once each fiscal year, the accounts shall be audited by properly qualified auditors, a statement of which must be submitted to the Executive Board for acceptance. Copies of the annual financial statement shall also be sent to the national member associations.

Section 3: *Financial Commitments.* Monetary commitments in excess of 500 florins Dutch money or its equivalent, must be approved in advance by the Executive Board.

BOARD OF GOVERNORS AMERICAN DIABETES ASSOCIATION

The newly-constituted Board of Governors began its work in San Francisco on June 18, 1954, by organizing and electing officers for the coming year. At this, its first meeting, a joint session was held with the Council of the American Diabetes Association.

The duties of Governors were broadly defined by the Council:

a. To be the senior delegate to the Assembly of Delegates.

b. To assist in the creation of Affiliate units as authorized by the Council of the American Diabetes Association.

c. To encourage and co-ordinate activities in the field of diabetes at a state level, including professional education, public education and case finding.

d. To establish liaison between the American Diabetes Association and its Affiliates, and the State and County Medical Societies and any other groups.

e. Any other duties designated by the Council of the American Diabetes Association.

Governors will play an increasingly important part in current as well as future planning of ADA activities. They will serve to co-ordinate all activities pertaining to diabetes in each state. Policies and programs of the national organization will be interpreted to local groups; local interests and needs will in turn be reflected to the Council by the Board of Governors.

Louis K. Alpert, M.D., of Washington, D. C., was elected Chairman of the Board, with Edwin W. Gates, M.D., of Niagara Falls, N. Y., Vice-chairman. Henry E. Oppenheimer, M.D., of St. Louis, Mo., was elected Secretary of the group. As Chairman, Dr. Alpert will serve as a member of the Council of the ADA ex-officio.

The following Governors to date have been appointed for one year.

State	*Governor*
Alabama	Leon S. Smelo, M.D.
Arizona	Eleanor Waskow, M.D.
Arkansas	James T. Wortham, M.D.
California	
Northern & Nevada	H. Clare Shepardson, M.D.
Southern	Helen E. Martin, M.D.
Colorado	W. Bernard Yegge, M.D.
Connecticut	Barnett Greenhouse, M.D.
Delaware	Lewis B. Flinn, M.D.
District of Columbia	Louis K. Alpert, M.D.
Florida	Sidney Davidson, M.D.
Georgia	Christopher J. McLoughlin, M.D.
Idaho	Samuel M. Poindexter, M.D.
Illinois	
Northern	Ford K. Hick, M.D.
Southern	Thomas D. Masters, M.D.
Indiana	John H. Warvel, M.D.
Iowa	Robert C. Hardin, M.D.
Kansas	Thomas J. Luellen, M.D.
Kentucky	Carlisle Morse, M.D.
Louisiana	Daniel W. Hayes, M.D.
Maine	Elton R. Blaisdell, M.D.
Maryland	J. Sheldon Eastland, M.D.
Massachusetts	Reed Harwood, M.D.
Michigan	William M. LeFevre, M.D.
Minnesota	Moses Barron, M.D.
Missouri	Henry E. Oppenheimer, M.D.
Montana	John A. Layne, M.D.
Nebraska	Morris Margolin, M.D.
Nevada	See Northern California
New Hampshire and Vermont	James H. Townsend, M.D.
New Jersey	Benjamin Saslow, M.D.
New York	
Eastern	Edmund L. Shlevin, M.D.
Western	Edwin W. Gates, M.D.
North Carolina	Charles W. Styron, M.D.
North Dakota	Edgar A. Haunz, M.D.
Ohio	Cecil Striker, M.D.
Oklahoma	Bert F. Keltz, M.D.
Oregon	Zolton T. Wirtschafter, M.D.
Pennsylvania	
Eastern	William F. Hanisek, M.D.
Western	John A. O'Donnell, M.D.
Rhode Island	Louis I. Kramer, M.D.
South Dakota	John W. Donahoe, M.D.
Tennessee	Philip C. Thomas, M.D.
Texas	Edmond K. Doak, M.D.
Utah	Donald E. Smith, M.D.
Vermont	See New Hampshire
Virginia	William R. Jordan, M.D.
Washington	Robert L. Reeves, M.D.
West Virginia	George P. Heffner, M.D.
Wisconsin	Maurice Hardgrove, M.D.

THE FIFTEENTH ANNUAL MEETING

Atlantic City, N. J., will play host to the American Diabetes Association at the 1955 Annual Meeting June 4-5, immediately preceding the Annual Session of the American Medical Association, June 6-10. ADA committees scheduled to convene before the Annual Meeting include: Assembly of Delegates, June 3; Board of

Governors, June 3; Council, June 3-4. Other Committees will meet prior to the Scientific Sessions.

Members who wish to attend the Annual Meeting are urged to make their reservations immediately. Individual rooms are being held for members, but there is no assurance that there will be sufficient accommodations for everyone.

Chalfonte-Haddon Hall will serve as headquarters for our Association. Members who wish to remain for the American Medical Association session must make reservations for June 6-10 through the Atlantic City Convention Bureau, 16 Central Pier, Atlantic City, N. J., either by letter or by filling out the reservation form appearing in the *Journal of the American Medical Association.* If you wish to stay for the A.M.A. session without changing hotels, the Convention Bureau has given reasonable assurance that reservations will be continued at Chalfonte-Haddon Hall if they are sent in promptly.

The Scientific Sessions of the American Diabetes Association will consist of a Joint Meeting with The Endocrine Society on Saturday afternoon, June 4, and our own scientific meeting Sunday morning and afternoon, June 5. Two panels will be held on Sunday: one at the conclusion of the morning sessions, entitled "Fluids and Electrolytes in Therapy," and the other at the conclusion of the afternoon session, entitled "What I Teach My Diabetic Patients."

Among the papers which will be presented are: "Correlative Studies of Serum Lipids and Polysaccharides in Diabetes Mellitus," by David Adlersberg and Chun-I Wang (by invitation), The Mount Sinai Hospital, New York; Harold Rifkin, James Berkman (by invitation) and George Ross (by invitation), Montefiore Hospital, New York; "The Relation of Portal Cirrhosis to Hemochromatosis and to Diabetes Mellitus," by E. T. Bell, University of Minnesota Medical School, Minneapolis, Minn.; "Glomerular Changes and Steroid Diabetes Produced by the Administration of Various Adrenal Steroids, Whole Adrenal Extract and Corticotropin to Rabbits," by J. M. B. Bloodworth, Jr., and George J. Hamwi, Ohio State University College of Medicine, Columbus, Ohio; "Recent Insurance Mortality Experience on Persons with (1) Glycosuria, and (2) Family History of Diabetes," by Mr. Herbert H. Marks, Chairman, Committee on Statistics, American Diabetes Association; "A Simple Enzymatic Determination of Glucose Using Glucose Oxidase," by R. E. Froesch (by invitation) and A. E. Renold, Harvard University, Department of Medicine, and Peter Bent Brigham Hospital, Boston, Mass.

THIRD STUDENT-INTERN ESSAY CONTEST

The American Diabetes Association is sponsoring a Third Student-Intern Essay Contest, with a closing date of May 10, 1955. Two awards will be made this year. A prize of $250, made possible by the generosity of the St. Louis Diabetes Association, will be given to the author or authors of the best paper reporting original laboratory research or clinical study. An additional award of $50 will be given anonymously by a member of the Association for the best review article or case report.

Candidates for either prize may select any subject relating to diabetes and basic metabolic problems. It is hoped that each year a larger number of young physicians will direct their study to diabetes and to the care of diabetic patients.

The contest is open to medical students or physicians within two years of graduation. Manuscripts should be submitted to the Editorial Office of DIABETES: *The Journal of the American Diabetes Association,* 1 East 45th Street, New York 17, New York.

NEW RESEARCH GRANT

The Council of the American Diabetes Association has accepted the sum of $7,500 from the Atlas Powder Company. This money is to be granted to individuals for research on the metabolism of sorbitol in the human diabetic.

Those interested will submit their outline of research (personnel, physical facilities, etc.) to the Chairman of the Committee on Research of the American Diabetes Association. This Committee will select the recipient(s) of this grant.

New Members

The following Active Members were elected as of Jan. 1 and Feb. 1, 1955:

Alabama	
Cohen, Robert S.	Birmingham
California	
Rowe, Albert, Jr.	Oakland
Tinney, Malcolm J.	Sacramento
Florida	
Steward, Williams D.	Orlando
Illinois	
Brewster, Edward S.	Danville
Indiana	
Murphy, Josephine F.	South Bend

Iowa	
Hegstrom, George J.	Ames
Read, Charles H.	Iowa City
Maine	
Bryant, Mason D., Jr.	Hallowell
Maryland	
Watson, George S.	Baltimore
Massachusetts	
Cohen, Alan S.	Boston
Smith, Herbert H.	Brookline
Michigan	
Bielawski, John G.	Detroit
Johnson, Robert D.	Ann Arbor
Moss, Harvey L.	Coldwater
Minnesota	
Flink, Edmund B.	Minneapolis
New York	
Burgeson, Paul A.	Warsaw
Carroll, John J.	Niagara Falls
Dyster, Melvin B.	Niagara Falls
Gurian, Harvey	Middletown
Roberts, Warren C.	Niagara Falls
Wallace, Robert B.	Utica
Ohio	
Gold, Arnold V.	Akron
Patterson, John W.	Cleveland
Oklahoma	
Tompkins, Robert G.	Tulsa
Pennsylvania	
Bove, Frank A.	Philadelphia
Dituri, Bessie	Philadelphia
Gundersen, Kare	Philadelphia
Zimmer, Frederick E.	Danville
Tennessee	
Hartung, Carl A.	Chattanooga
Texas	
Ibarra, Jesse D., Jr.	Temple
McMillan, Charles D.	Temple
Wisconsin	
Junkerman, Charles L.	Milwaukee

OTHER COUNTRIES

Argentina	
Houssay, Alberto B.	Buenos Aires
Canada	
Aras, Kazim	Toronto
Germany	
Appel, Walter	Kiel
Italy	
Iannaccone, Angelo	Naples
Sweden	
Engleson, Gunnar H.	Lund
Grönberg, Albert E.	Vanersborg den
Switzerland	
Muller, Doris H.	Winterthur

The following Associate Member was elected as of Feb. 1, 1955:

Pennsylvania	
Shaler, Amos	State College

News of Affiliate Associations

The CHICAGO DIABETES ASSOCIATION held a joint meeting with the Chicago Gynecological Society and the Chicago Pediatric Society Nov. 19, 1954. The Scientific Program included: "The Use of Female Sex Hormones in the Management of the Pregnant Diabetic," by Priscilla White, M.D.; "The Newborn of Diabetic Mothers," by Alvah Newcomb, M.D., with Matthew M. Steiner, M.D., as discussant; "The Significance of Renal Glycosuria in Pregnancy," by Jerome T. Paul, M.D., with Arthur R. Colwell, M.D., as discussant. Dr. Newcomb is President and Dr. Paul Secretary of the Chicago Diabetes Association.

The NEW JERSEY DIABETES ASSOCIATION, in co-operation with the New Jersey State Department of Health, held its Second Annual Symposium on Diabetes Mellitus Oct. 27, 1954. Joseph Skwirsky, M.D., served as Session Chairman for Part I of the program, which included: Introduction by George M. Knowles, M.D., President of the New Jersey Diabetes Association; "Diabetes, A Public Health Program," by Daniel Bergsma, M.D., State Commissioner of Health; "Diabetic Retinopathy," by Arthur Linksz, M.D.; "Diabetic Nephropathy," by Harold M. Rifkin, M.D.; "Diabetes in Children," by Priscilla White, M.D.; and "Vascular Surgical Complication in Diabetes Mellitus," by Gerald H. Pratt, M.D. Otto Brandman, M.D., was Session Chairman for Part II, a Panel Discussion by Drs. Linksz, Rifkin, White, and Pratt. The Panel was moderated by Benjamin Saslow, M.D., Governor of the American Diabetes Association for New Jersey.

The New Jersey Diabetes Association (Clinical Society), in co-operation with The New Jersey Academy of General Practice, will present another Symposium on Diabetes Mellitus Jan. 19, 1955. The program includes: "Treatment of Diabetes Mellitus," by Herbert

M. Pollack, M.D.; and "Diabetic Coma," by Maurice Brueger, M.D.

In April, the Section on Metabolism, Medical Society of New Jersey, will present: "The Problem of Obesity," by Garfield G. Duncan, M.D.; "Insulin in Clinical Medicine," by William A. Nyiri, M.D.; "Extrapancreatic Diabetes," by Herbert S. Kupperman, M.D.; and "Hepatic Coma in Portal Cirrhosis," by Victor A. Bressler, M.D. The Clinical Society of the New Jersey Diabetes Association has been invited to attend the luncheon of the Section on Metabolism of the Medical Society of New Jersey April 20, after the meeting of that Section at the Ambassador Hotel in Atlantic City.

The NEW YORK DIABETES ASSOCIATION observed the twentieth year of its founding on December 26. Appropriate ceremonies for celebrating this event will be held in the Spring to coincide with the annual fund-raising campaign.

At the Annual Meeting of the Board of Directors of the New York Diabetes Association, the Camp NYDA medal was awarded to Fred Allen, Ham Fisher, and William Talbert in recognition of their services for the diabetic children of the greater New York area.

The Clinical Society of the New York Diabetes Association and The New York Academy of Medicine Section on Medicine will hold a combined meeting March 15, 1955, at the New York Academy of Medicine Building, New York City. Joseph P. Hoet, M.D., will speak on "The Diabetogenic Action of Pregnancy." Discussion will include Alfred E. Fischer, M.D., and Hugh L. C. Wilkerson, M.D. Chairman of the Section on Medicine is Edward Tolstoi, M.D., and Secretary, Charles A. Poindexter, M.D. Chairman of the Clinical Society of the New York Diabetes Association is Murray M. Levites, M.D., and Secretary-Treasurer, Lawrence E. Hinkle, Jr., M.D. Irving Graef, M.D., is Chairman of the Committee on Professional Education.

News Notes

First Annual McLester Award

Grace Bulman, Director, Dietetic Service, of the Veterans Administration, was chosen to receive the first annual James Somerville McLester Award "for distinguished service in the field of applied nutrition and dietetics." She received a bronze plaque and a $500 prize for her long years of outstanding service and accomplishment in the dietary care and nutritional betterment of the hundreds of thousands of Army, Navy, Marine, and Coast Guard veterans, who are patients in the 172 Veterans Administration Hospitals she serves.

The McLester Award honors the memory of the late Col. James Somerville McLester, a former President of the American Medical Association and leading authority in the science of nutrition and metabolism. Sponsor of the award is Chas. Pfizer & Co., Inc., of Brooklyn, N. Y.

1955 National Health Forum

The 1955 National Health Forum, to be held March 23 and 24, 1955, at the Hotel Sheraton Astor, New York, N. Y., will concern itself with "Forecasting America's Health," according to A. W. Dent, President of the National Health Council. The 48 national organization members of the Council annually sponsor the Forum. Roscoe P. Kandle, M.D., Deputy Commissioner of the New York City Department of Health, is chairman of the Forum Committee.

Information concerning the program may be obtained from The National Health Council, 1790 Broadway, New York 19, N. Y. The American Diabetes Association is an Active Member of the Council.

$10.2 Million Grants Approved for Research

The Public Health Service has announced approval of grants totaling $10,275,533 for support of 972 medical research projects. Awards were based on recommendations made to Surgeon General Leonard A. Scheele following October-November meetings of the seven national advisory councils to the National Institutes of Health. The sum represents approximately 30 per cent of the $33.9 million appropriated by Congress for assistance to medical research in the fiscal year ending June 30, 1955. Grants for research in arthritis and metabolic diseases amounted to $998,703 for 107 projects.

Personals

JERE M. BAUER, M.D., has become Associate Professor of Internal Medicine at the University of Michigan.

JOSEPH T. BEARDWOOD, JR., M.D., Chairman of the Association's Committee on Employment, spoke on "The Problem of Overweight in Industry" at the 19th Annual Meeting of the Industrial Hygiene Foundation, November 17, at the Mellon Institute, Pittsburgh, Pa.

CHARLES H. BEST, M.D., Director of the Banting and Best Department of Medical Research and Professor of Physiology at the University of Toronto, has been elected to the Board of Scientific Directors of the Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine.

GROSVERNOR W. BISSELL, M.D., Buffalo, N. Y., discussed "Latest Trends in Hormone Therapy" at the annual conference of the American Association of Medical Record Librarians in Detroit, Oct. 4-8, 1954.

EDWARD L. BORTZ, M.D., is Director of the Postgraduate Course on "Stress and Aging" arranged by The American College of Physicians at The Lankenau Hospital, Philadelphia, Pa., April 20-23. DR. BORTZ, ERNEST M. BROWN, JR., M.D., E. STERLING NICHOL, M.D., and SALVADOR ZUBIRAN, M.D., are among Officers of Instruction for the Course. Members of the American Diabetes Association who will take part in other Postgraduate Courses of the College include MAURICE BRUGER, M.D., LAWRENCE E. HINKLE, JR., M.D., and GERALD H. PRATT, M.D., who are Officers of Instruction for another course, "Diseases of the Blood Vessels and Problems of Thromboembolism," to be held March 14-18 at Cornell University Medical College and The New York Hospital, New York, N. Y.

JAMES R. COOK, M.D., formerly on the staff of Cleveland Clinic at Cleveland, Ohio, entered private practice in Orlando, Fla., Oct. 1, 1954, and is a member of the staff of the Orange Memorial Hospital there.

GEORGE W. DANA, M.D., has accepted the appointment of Medical Director of the Bingham Associates Fund at the New England Medical Center in Boston. He also has a full-time appointment as Assistant Professor of Medicine at Tufts College School of Medicine. Dr. Dana was formerly Associate Dean of the Johns Hopkins Medical School and Director of the Medical Care Clinic of the Johns Hopkins Hospital.

EDWIN J. DE COSTA, M.D., Chicago, Ill., was a member of the Monday Symposium on Medical Complications of Pregnancy at the Sixth American Congress on Obstetrics and Gynecology, Dec. 13-17, 1954, at The Palmer House in Chicago. His subject was "Diabetes in Pregnancy." CHARLES FLOWERS, JR., M.D., Chapel Hill, N. C., WILBUR F. MANLY, M.D., Denver, Col., EDWARD TOLSTOI, M.D., New York, N. Y., and PRISCILLA WHITE, M.D., Boston, Mass., spoke on the same subject at later meetings. Drs. Flowers, Manly and White also spoke at Breakfast Conferences held at 7:30 a.m. on Tuesday, Wednesday and Thursday during the Congress.

ELLIOTT P. JOSLIN, M.D., Honorary President, American Diabetes Association, will give the Banting Memorial Lecture of the British Diabetic Association in Cambridge, England, July 4, 1955, at 3:30 p.m. The Lecture, entitled "Diabetes for Diabetics," coincides with the opening day of the Second Congress of the International Diabetes Federation, which will be held in the same city.

ELLIOTT P. JOSLIN, M.D., HOWARD F. ROOT, M.D., and PRISCILLA WHITE, M.D., Boston, were the participants in a Symposium on Diabetes (Aspects in Children, Pregnancy, and Surgery) at the Annual Scientific Assembly and Congress of the New York Academy of General Practice held in Syracuse, New York, Oct. 11-13, 1954.

Obituaries

JOSE N. GANDARA, M.D., of Santurce, Puerto Rico, died suddenly Oct. 12, 1954, while attending a conference in Philadelphia, Pa. Dr. Gandara, who was born in Ponce, Puerto Rico, Aug. 26, 1907, received his premedical training at New York University and obtained his medical degree from Long Island College of Medicine in 1933. He served an internship at the San Juan Presbyterian Hospital in Puerto Rico. Dr. Gandara was President of the Puerto Rico Medical Association, and a member of important committees. He was a member of the medical staff of the University, Presbyterian, San Juan City, Doctors, San Jose and Pereira Leal Hospitals, and Clinical Professor of Medicine in the School of Medicine of the University of Puerto Rico. In addition to his membership in the American Diabetes Association, Dr. Gandara was President of the Puerto Rican chapter of the American Heart Association.

FLOYD L. ROGERS, M.D., of Lincoln, Nebraska, died Nov. 30, 1954. With the death of Dr. Rogers, the medical profession lost one of its outstanding leaders in Nebraska. Dr. Rogers served a term as President of the Nebraska State Medical Association. He was also Chairman of the Committee on Medical Education and a leader in other activities of this Association. He became a member of the American Diabetes Association in 1946, and was President of the West Central Diabetes Associa-

tion in 1952-1953. In 1951 he organized and conducted the Springdale Camp for Diabetic Children.

Dr. Rogers was born in Le Mars, Iowa, in 1896. He graduated from Northwestern University College of Medicine and was subsequently certified as a specialist by the American Board of Internal Medicine. He became a Fellow of the American College of Physicians, and was Clinical Associate Professor in Internal Medicine at the University of Nebraska School of Medicine. He is survived by his wife and two daughters.

JAMES WINN SHERRILL, M.D., of La Jolla, California, died Jan. 4, 1955. Dr. Sherrill had been Medical Director of The Scripps Metabolic Clinic, La Jolla, Calif., continuously since its founding in 1924. He was born in Temple, Texas, April 22, 1890, and received a Bachelor of Science degree from Baylor University in 1913 and his medical degree four years later from Johns Hopkins University. He was a Lecturer in Medicine at the Medical School of the University of California, Berkeley, California, and a Lecturer in Diseases of Metabolism in the United States Naval Hospital in San Diego. In the last year of World War I, he was a lieutenant in the Medical Corps of the Army.

From 1922 to 1924, Dr. Sherrill was associated with F. M. Allen, M.D., at the Rockefeller Institute, New York City, in early animal experimental work in diabetes mellitus. He was the author of numerous articles dealing with diabetes.

In addition to membership in the American Diabetes Association, he was a Fellow of the American College of Physicians, a Diplomate of the American Board of Internal Medicine, and a member of the Association for the Study of Internal Secretions. He is survived by his wife and two children.

Word has been received of the death Aug. 22, 1954, of WALTER I. WERNER, M.D., a member of the American Diabetes Association since October 1951. Dr. Werner was born Feb. 2, 1898, in Covington, Kentucky. He attended Fordham University in New York and the University of Maryland, receiving the degree of M.D. from the latter in 1923. He spent two years at Mt. Sinai Hospital in Cleveland and five years at the William H. Maybury Sanatorium, Northville, Michigan. In 1930 he was appointed Medical Director of the Oakland County Tuberculosis Sanatorium in Pontiac, Michigan. He entered the private practice of internal medicine in Albuquerque, New Mexico, in 1934, and became Director of Clinical Research in the Maytag Hospital in 1935. After World War II he became a Consultant in Internal Medicine at the Veterans Hospital. He was also associated with St. Joseph's Hospital and the Presbyterian Hospital in Albuquerque. He was appointed Medical Advisor to the New Mexico Tuberculosis Sanatorium in Socorro, New Mexico, in 1953.

Dr. Werner was a licentiate of the American Board of Internal Medicine. He became a Fellow of the American College of Physicians in 1941 and Governor of the College for the State of New Mexico in 1949. Dr. Werner was active in many medical organizations. In addition to his membership in the American Diabetes Association, he was also a member of the American Heart Association, the South Western Allergy Forum, the National Tuberculosis Association, and the Trudeau Society.

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